IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH,	)	Civil Action
Plaintiffs,	)	
v.	)	
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	No. 15-1102-GMS

- - -

Wilmington, Delaware
Tuesday, January 30, 2018
9:00 a.m.
Trial Day 2

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Senior Judge, U.S.D.C., District of Delaware

APPEARANCES:

JACK B. BLUMENFELD, ESQ., and
DAREN J. FAHNESTOCK, ESQ.
Morris, Nichols, Arsht & Tunnell LLP
-and-
EDGAR H. HAUG, ESQ.,
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KAREN E. KELLER, ESQ.
Shaw Keller LLP
-and-
DARYL L. WIESEN, ESQ.
WILLIAM G. JAMES, ESQ.,
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(Washington, DC)

Counsel for Defendant

- - -

08:29:19
08:29:19

09:02:51

09:02:51 THE COURT: Good morning, please, take your
09:02:52 seats.
09:02:53 (Counsel respond "Good morning.")
09:02:54 MR. WIESEN: Dr. Burch is on his way in, Your
09:03:16 Honor.
09:03:16 THE COURT: Good morning, Dr. Burch.
09:03:18 THE WITNESS: Good morning, Your Honor.
09:03:22 .... RONALD BURCH, having been previously sworn
09:03:26 as a witness, was examined and testified further as
09:03:29 follows ...
09:03:31 CROSS-EXAMINATION CONTINUED
09:03:32 Q. Good morning, Dr. Burch.
09:03:34 A. Good morning.
09:03:34 Q. I have a few more questions this morning.
09:03:37 A. All right.
09:03:38 Q. Yesterday you testified about some financing problems
09:03:44 that Nova was having. Do you recall that?
09:03:48 A. Yes, I do.
09:03:49 Q. The financing of the bradykinin antagonist program was
09:03:52 a concern to you. Isn't that correct?
09:03:55 A. Financing overall was what concerned me.
09:03:58 Q. You were also concerned specifically about financing
09:04:05 the bradykinin program. Right?
09:04:07 A. For the company it was a general concern. For me I
09:04:12 was trying to triage the projects.

09:04:14 Q. **In fact, while you were at Nova, you actually**
09:04:17 **recommended to Nova upper management that the bradykinin**
09:04:20 **antagonist program be discontinued. Is that correct?**
09:04:23 A. **I did, yes.**
09:04:09 Q. **And you made that recommendation in late 1990; isn't**
09:04:16 **that right?**
09:04:16 A. **Yes.**
09:04:16 Q. **And did your change in thinking about the priority of**
09:04:23 **the bradykinin antagonist program result from anything that**
09:04:27 **had to do with competitors in the bradykinin program?**
09:04:32 A. **No. When I made the recommendation, I wasn't aware of**
09:04:39 **Hoechst.**
09:04:41 Q. **And wasn't it your recommendation to stop the**
09:04:44 **bradykinin antagonist program motivated by the fact that the**
09:04:49 **Leumedins Program was more commercially interesting at the**
09:04:52 **time?**
09:04:52 A. **The Leumedins Program was much more popular, yes,**
09:04:56 **that's right.**
09:04:57 Q. **Would you please turn to tab 3 in your binder. Are**
09:05:11 **you there?**
09:05:12 A. **Yes.**
09:05:12 Q. **Thank you.**
09:05:14 **Are you familiar with this document, which is a**
09:05:20 **pink sheet?**
09:05:21 A. **I don't specifically recall it, but there were a**

09:05:23 number of press releases at the time.
09:05:24 Q. All right. You know what a pink sheet is; is that
09:05:26 right?
09:05:27 A. Yes.
09:05:27 Q. All right. If you would please, I invite your
09:05:30 attention to line 8.
09:05:38 A. All right.
09:05:38 Q. I'd like to read. "By coincidence, Nova announced the
09:05:45 Leumedins research almost one year to the day after dropping
09:05:49 work on its high profile bradykinin clinical program."
09:05:55 Did I read that correctly?
09:05:56 A. You did.
09:05:58 Q. Does that refresh your recollection about the fact
09:06:00 that Nova dropped their high profile bradykinin clinical
09:06:04 program as set forth in this press release?
09:06:06 A. This is -- the press release here is referring to the
09:06:09 NPC 567 clinical trial.
09:06:14 Q. Is that what that's referring to?
09:06:15 A. Yes.
09:06:16 Q. And isn't it, isn't it -- do you recall when the
09:06:21 Leumedins Program -- withdrawn.
09:06:25 If you go up to the third line in this
09:06:27 document -- actually, I will go to the second line. I will
09:06:36 start with the first line so we have it in context.
09:06:38 "Nova's topical leumedin compound in Phase II

09:06:43 **for contact dermatitis, the company announced at a**
09:06:46 **January 17th press conference showcasing the firm's**
09:06:49 **proprietary class of novel anti-inflammatory compounds.**
09:06:52 **Efficacy trials of the topical Leumedin compound, designated**
09:06:56 **NPC 15199 are expected to continue through 1991. The IND**
09:07:03 **was filed in April 1990 and Phase I trials were completed in**
09:07:09 **the fourth quarter."**
09:07:10 **Did I read that correctly?**
09:07:12 A. **Yes, you did.**
09:07:14 Q. **Does that seem accurate to you as to what was**
09:07:16 **happening in 1990?**
09:07:17 A. **That does.**
09:07:18 Q. **'91. It does?**
09:07:19 A. **Yes.**
09:07:20 Q. **Thank you.**
09:07:22 **I would like you to now turn to tab 2 in your**
09:07:38 **binder.**
09:07:43 **Do you recognize this article?**
09:07:44 A. **I do.**
09:07:44 Q. **Are you an author on this article?**
09:07:46 A. **I am.**
09:07:48 Q. **The article is entitled biochemical and molecular**
09:07:50 **pharmacology of kinin receptors. Is that right?**
09:07:54 A. **Yes.**
09:07:54 Q. **Do you see a date when this is published?**

09:07:57 A. **1992.**

09:07:58 Q. **If you would please now turn to Page 527 of your article, and we're still on tab 2. I'm going to read the first two sentences of the second full paragraph.**

09:08:18 **Are you with me?**

09:08:20 A. **I am.**

09:08:21 Q. **Okay. Thank you.**

09:08:22 **"Recently, Hock and colleagues have described a series of decapeptides containing the modified amino acids D-Tic (1, 2, 3, 4-tetrahydroisoquinnoline-3-carboxylic acid) and LOic (octahydroindole carboxylic acid) as replacements for the 7 and 8 positions in the primary amino acid sequence of NPC567-like peptides (74, 102). These decapeptides, highly constrained in their C-terminal portions, were the first examples of a new generation of potent BK receptor antagonists that were several hundred times more potent than [DPhe7]-substituted BK analogs in guinea pig ileum. In an effort to quantify the conformational impact of the C-terminal substituents within these peptides, a systematic ten-degree grid search was performed on model dipeptides derived from those of the Hoechst group (100)."**

09:09:40 **Did I read that correctly?**

09:09:41 A. **You did.**

09:09:43 Q. **Isn't it correct that what you're describing here is the conformationally constrained decapeptides of Hock and**

09:09:47

09:09:51 colleagues having D-Tic at seven position and L-Oic at the
09:09:56 eight position as the first examples of a new generation of
09:10:00 potent bradykinin antagonists?
09:10:03 A. Yes, that's right.
09:10:03 Q. That's what you are reporting. Right? I read the
09:10:10 next sentence.
09:10:11 Dr. Burch, what is a systematic ten grid search?
09:10:17 Do you know?
09:10:18 A. We were doing a molecular model, looking at energy
09:10:22 minimum for the conformations.
09:10:23 Q. And, Dr. Burch, in this article you say the systematic
09:10:26 ten grid search was performed on model dipeptides derived
09:10:31 from those at the Hoechst group.
09:10:32 Can you recall which model dipeptides were
09:10:34 derived from the Hoechst group?
09:10:36 A. I don't recall as I sit here, but my guess is they
09:10:41 were the D-Tic seven, Oic eight, and perhaps some of the
09:10:45 other eight position.
09:10:45 Q. The section that I read to you ends with a reference
09:10:50 to 100. If you could go to the end of the article, can you
09:10:56 tell us what 100 is?
09:10:57 A. 100 is a paper by Dr. Kyle, other members of Nova and
09:11:13 myself.
09:11:14 Q. And yourself?
09:11:15 A. Yes.

09:11:15 Q. **Is that JTX-9 as we've been talking about in this**
09:11:19 **case?**
09:11:22 A. **It's one of the papers we discussed in the case, yes.**
09:11:25 Q. **I'd like you to now turn to JTX-9, please.**
09:11:35 **Now, this is your article; right?**
09:11:36 A. **JTX-9?**
09:11:38 Q. **JTX-09?**
09:11:40 A. **All right. Yes.**
09:11:41 Q. **Do you have that? All right. This is your article;**
09:11:46 **right?**
09:11:46 A. **It is.**
09:11:46 Q. **And I would like to go to 9.4, please. JTX 9.4.**
09:11:55 **And let me go down to where it says about --**
09:12:06 **it's the first indented paragraph that says, to quantify.**
09:12:10 **Do you see that?**
09:12:10 A. **Yes, I do.**
09:12:12 Q. **I have it highlighted. All right. So let me read.**
09:12:16 **To quantify the conformational impact of the C-terminal**
09:12:19 **substituents within these peptides, a systematic ten degree**
09:12:23 **grid search was performed on three model compounds IA, IIA,**
09:12:27 **and IIIA, shown in Figure 2.**
09:12:30 **Did I read that correctly?**
09:12:31 A. **You did.**
09:12:32 Q. **Please turn to Figure 2 of the JTX-09 article. And**
09:12:37 **can you identify which model dipeptides are shown there?**

09:12:40 A. **Those are D-Tic-Tic, D-Tic-D-Tic, and D-Tic-Aoc.**

09:12:54 Q. **IA is what, D-Tic and Tic? Is that what you said?**

09:12:58 A. **IA is D-Tic, L Tic.**

09:13:01 Q. **So referring back to your article in tab 2 --**

09:13:04 A. **Yes.**

09:13:04 Q. **-- which we just looked at, isn't it the case that you do characterize these dipeptides as derived from the Hoechst group in the article that you wrote?**

09:13:14 A. **Yes.**

09:13:16 Q. **And, Dr. Burch, isn't the dipeptide illustrated in Figure 2 in JTX-09 dipeptide IA, which is D-Tic and Tic, the two amino acids of the seven and eight position of peptide one, which you have already identified as NPC 16731?**

09:13:37 A. **Yes.**

09:13:38 Q. **So mustn't it be the case that the substitutions made at the 7 and 8 position of NPC 16731 were derived from substitutions made by the Hoechst group?**

09:13:50 A. **As I testified yesterday, as indicated in this paper, we did confirm Hoechst had already filed patents.**

09:13:58 Q. **Is that a yes?**

09:13:59 A. **Yes.**

09:14:00 Q. **Thank you.**

09:14:04 **And if the substitutions made at the 7 and 8 position of NPC 16731 were derived from substitutions made by the Hoechst group, isn't it also the case Nova could not**

09:14:10

09:14:15 have developed 16731 independently and coincidentally?
09:14:20 A. Developed clinically toward commercialization? The
09:14:24 clarification. You said we couldn't have developed them.
09:14:27 You meant clinically and commercially.
09:14:29 Q. I meant independently and coincidentally, which are
09:14:33 the words used in your article?
09:14:34 A. Oh, I see, no. The words used in the article indicate
09:14:37 that we had made those and then we found out that Hoechst
09:14:41 had already made them.
09:14:42 Q. Now, Dr. Burch, you've testified about a number of
09:14:49 events that you say happened maybe 27, 28 years ago; isn't
09:14:56 that right?
09:14:56 A. That's correct.
09:14:57 Q. For example, you went to a conference and you talked
09:14:59 about what you saw at the conference 28 years ago?
09:15:02 A. Yes.
09:15:03 Q. And you also talked about what was being developed at
09:15:06 Nova also 27, 28 years ago; isn't that right?
09:15:10 A. That's correct.
09:15:10 Q. And other than the articles that we've seen here,
09:15:13 do you have any documents whatsoever to support anything
09:15:17 that you say based on what you recall happened 27, 28 years
09:15:21 ago?
09:15:21 A. I don't have any documents in my possession other than
09:15:25 the articles that were published.

09:15:27 **MR. HAUG: Thank you. No further questions, Your Honor.**

09:15:29 **THE COURT: All right. Redirect?**

09:15:31 **MR. WIESEN: Just briefly, Your Honor.**

09:15:37 **REDIRECT EXAMINATION**

09:15:38 **BY MR. WIESEN:**

09:15:45 Q. **If you could turn to, in your cross binder, the binder Mr. Haug just showed you --**

09:15:48 A. **All right.**

09:15:49 Q. **-- to tab 3.**

09:15:50 **MR. WIESEN: Your Honor, unfortunately, I don't have this one electronically, but it will just be very brief.**

09:15:53 **THE COURT: What tab?**

09:15:57 **MR. WIESEN: Tab 3.**

09:15:58 **THE COURT: Okay.**

09:15:59 **BY MR. WIESEN:**

09:15:59 Q. **Mr. Burch, on that pink sheet, about the leumedins program?**

09:16:00 A. **Yes.**

09:16:03 Q. **Do you recall that direct? Let me read it back into the record. By coincidence, Nova announced the leumedins research almost one year to the day after dropping work on its high profile bradykinin clinical program.**

09:16:04 A. **Yes.**

09:16:17 Q. **Do you see that?**

09:16:18 A. **I see that.**

09:16:19 Q. **Could you explain what that meant?**

09:16:22 A. **Yes. So as I testified yesterday, Nova had placed NPC 567 into a number of proof of concept trials. Some of those were topical trials looking at pain. Others were inhaled trials looking at both airways' hyperreactivity.**

09:16:43 Q. **And so was it the case that Nova had shut down the bradykinin program entirely in 1990?**

09:16:50 A. **No. The trials for NPC567 had all ended by that point.**

09:16:56 Q. **Could you go back then just to JTX-9. If we could have that. And if we have Figure 1 in the upper left-hand corner of 9.3.**

09:17:12 A. **Yes.**

09:17:13 Q. **Dr. Burch, had you seen any of Hoechst's work when Nova first identified these sequences and peptides that are in Figure 1 of JTX-9?**

09:17:30 A. **I have not.**

09:17:32 Q. **Do you know if anybody at -- as far as you know, had anybody at Nova?**

09:17:36 A. **No.**

09:17:37 **MR. WIESEN: No further questions, Your Honor.**

09:17:38 **THE COURT: Thank you. Doctor, please be careful stepping down.**

09:17:40

09:17:40 THE WITNESS: Thank you.

09:17:41 (Witness excused.)

09:17:55 MR. WIESEN: Your Honor, our next witness is going to be Dr. Knolle, who will be a videotaped deposition.

09:18:06 Dr. Knolle is the former Hoechst and Jerini employee, one of the named inventors on the '333 and 7,803 patents. He was the head of the laboratory at Hoechst in the eighties and nineties and then the head of R&D at Jerini. He was the one that who was going to come live and has taken ill in Germany, so he can't be here.

09:18:30 The deposition is a little over an hour, maybe and hour and ten minutes. About 15 minutes from the defendant, (check) because they were going to bring him live, so they have more testimony from him.

09:18:39 THE COURT: Okay.

09:18:40 MR. WIESEN: We should have clip reports, I think, that we can hand up.

09:18:46 THE COURT: It is what it is.

09:19:18 (The videotaped deposition of Jochen Knolle was played as follows.)

09:19:19 "Question: Could you please state and spell your name for the record?

09:19:21 "Answer: My last name is Knolle, K-n-o-l-l-e. First name is Jochen, J-o-c-h-e-n.

09:19:29 "Question: And what is your current address?

09:19:34 "Answer: Wetteraustrasse -- that is
09:19:40 W-e-t-t-e-r-a-u-s-t-r-a-s-s-e -- 25 Frankfurt Am Main,
09:19:45 Germany.
09:19:47 "Question: And is there any reason why you
09:19:49 can't give full and accurate and truthful testimony today?
09:19:53 "Answer: No, there's no reason.
09:19:55 "Question: Can you tell me about your education
09:20:00 since you graduated from high school, or the equivalent of
09:20:03 high school?
09:20:04 "Answer: So after gymnasium, I went to study
09:20:06 chemistry in Goettingen. Then I did my Ph.D. in the organic
09:20:14 chemistry department of Muenster, and then I proceeded to
09:20:19 E.J. Corey's Lab, the Nobel Prize winner in chemistry, in
09:20:25 Harvard, and then I started -- in January 1978 I started my
09:20:30 work at Hoechst.
09:20:31 "Question: And I apologize today I'm going to
09:20:39 ask you to clarify the things that you said many times. I'm
09:20:44 hindered by the fact that I am American and I don't speak
09:20:46 very good English, so if you could just tell me again, you
09:20:51 got your chemistry degree at what university, and could you
09:20:54 spell it for me?
09:20:57 "Answer: Goettingen is the diploma,
09:20:59 G-o-e-t-t-i-n-g-e-n and the Ph.D. in Muenster, Muenster is
09:21:06 written M-u-e-n-s-t-e-r.
09:21:11 "Question: And then you went to Harvard to

study with E.J. Corey?

"Answer: Yes, that's right.

"Question: And your Ph.D. was in synthetic organic chemistry?

"Answer: Yes, synthetic organic chemistry.

"Question: And what were you studying with Dr. Corey?

"Answer: I worked on the arachidonic cascade Thromboxane B2 synthesis and 12 HETE, the first oxidation product of arachidonic acid. 12HETE. That's an abbreviation for the arachidonic acid.

"Question: How long were you in Dr. Corey's lab?

"Answer: I don't know now, near two years -- not complete two years.

"Question: And you left Harvard and came back to Germany to join Hoechst?

"Answer: Yes.

"Question: I believe you said that you joined Hoechst in 1978?

"Answer: Yes, January 1, 1978.

"Question: What was your first position at Hoechst?

"Answer: Head of a laboratory.

"Question: Laboratory?

09:22:35 "Answer: Medicinal chemistry laboratory.

09:22:40 "Question: Did you consider yourself a medicinal chemist?

09:22:42 "Answer: I considered myself at that time a synthetic organic chemist focused on natural products.

09:22:44 "Question: What was your title in January 1978?

09:22:46 "Answer: I think head of laboratory.

09:22:50 "Question: Head of laboratory?

09:22:57 "Answer: Something like that, yes.

09:23:01 "Question: Approximately 1982, you mentioned that you started working on peptides and emergent nucleotides, did I get that right?

09:23:04 "Answer: There was a, due to the upcoming gene technology, there was a drive to synthesize oligonucleotides, the larger oligonucleotides and we established a department around 20 people maybe for the oligonucleotide group, and we had around 25, 30, 30 maybe even more people in the peptide group. And I was asked to move there to help this group and to later on, when the current director would retire, to take his job.

09:23:07 "Question: Did you actually have to physically move when you changed from ACE inhibitors?

09:23:09 "Answer: I moved from storey 1 to storey 3, same building.

09:23:13 "Question: And were you working in both the

09:23:16

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09:24:17 group doing synthetic oligonucleotide work and the peptide
09:24:23 work?
09:24:23 "Answer. No, but they reported to me. There's
09:24:25 a synthetic oligonucleotide group had reported to me.
09:24:30 "Question: And the peptide group reported to
09:24:32 you as well?
"Answer: Yes.
09:24:34 "Question: And what was your title during that
09:24:35 time, after 82?
09:24:38 "Answer: I think it sounds very militaristic --
hauptgruppenfuehrer.
09:24:48 "Question: Nice. What's that in English?
09:24:51 "Answer: I would -- a modern translation would
09:24:53 be, I would say, a director of a department, but my contract
09:24:57 said hauptgruppenfuehrer --
09:25:02 "Question: Director of peptide and
09:25:09 oligonucleotides?
"Answer: Yes.
09:25:12 "Question: And how long did you have that
09:25:13 position?
09:25:14 "Answer: Until I left. I didn't want to move
09:25:16 out of research.
09:25:17 "Question: So do I understand correctly that in
09:25:20 that 1982 time frame, you had approximately 50 people
09:25:28 reporting to you?

09:25:29 "Answer: With variations up and down, but approximately in this area -- so that's technician, engineers, and so on and Ph.D., and so on.

09:25:47 "Question: When did you leave Hoechst?

09:25:49 "Answer: I think I left somewhere in 1998. I don't recall exactly if it was in spring or summer. I don't -- I have to look it up.

09:25:57 "Question: So what did you do in 1998? Did you change jobs?

09:26:05 "Answer: I changed jobs to the U.S.

09:26:10 "Question: To where?

09:26:11 "Answer: San Francisco.

09:26:12 "Question: To go to work for Axys?

"Answer: Yes.

09:26:18 "Question: How long did you work there?

09:26:20 "Answer: I think 2000 somewhere, 2000 March or April or so on.

09:26:24 "Question: So approximately two years?

"Answer: Yes.

09:26:32 "Question: What did you do at Axys?

09:26:35 "Answer: I was responsible for the vice president -- I don't know any more the real title, I forgot, but basically, it was being responsible for the structural biology and the med chem effort.

09:26:49 "Question: And after Axys, where did you move

09:26:52 to?

09:26:53 "Answer: I went together with a friend, Jerini.
09:26:59 He was a friend of mine and we said that we want to move, or
09:27:06 establish a drug discovery development in Jerini, which was
09:27:12 at that time a pure peptide play for displaying peptides on
09:27:16 membranes, paper membranes.

09:27:19 "Question: The name of the company you moved to
09:27:28 was Jerini?

"Answer: Yes.

09:27:31 "Question: And it was an ongoing company when
09:27:35 you moved there?

09:27:36 "Answer: Yes. It was a small operation."

09:27:40 (Videotape paused.)

09:27:42 THE COURT: Is there anything you can do about
09:27:43 the noise, the background noise?

09:27:45 MR. WIESEN: Apparently, it's on the video, Your
09:27:47 Honor.

09:27:47 THE COURT: That's right. Okay. Let's go.

09:27:54 MR. WIESEN: I understand it gets better.

09:27:57 THE COURT: I hope so. It's distracting.

09:27:59 MR. WIESEN: I agree, Your Honor. I apologize.

09:28:03 THE COURT: All right. Go ahead.

09:28:06 (Videotape resumed.)

09:28:06 "Question: Where was it headquartered?

09:28:08 "Answer: In Berlin.

09:28:09 "Question: Did you move to Berlin?

"Answer: Yes.

09:28:12 "Question: Who was the friend that you moved
09:28:14 there with?

09:28:15 "Answer: He is a CEO. He was a founder of
09:28:18 Jerini, Jens Schneider-Mergener.

09:28:23 "Question: How long were you at Jerini?

09:28:26 "Answer: Until we sold it to Shire, to the end.
09:28:29 I believe eight years -- seven, eight years.

09:28:31 "Question: So you joined Jerini in
09:28:34 approximately 2000?

09:28:42 "Answer: I think officially I joined it in
09:28:44 November, I believe I got the first check from Jerini, or
09:28:50 they paid my relocation from San Francisco to Berlin. I
09:28:55 don't know, I don't remember anymore.

09:28:56 "Question: You said November -- November 2000?

09:29:01 "Answer: November 2000, yes.

09:29:02 "Question: When did you sell the company to
09:29:10 Shire?

09:29:12 "Answer: We sold it 2 July 2008 and I left, as
09:29:16 the other board members, officially on I think end of
09:29:19 October when the deal was closed, or finalized. The whole
09:29:24 managing board stepped down. It was part of the deal.

09:29:33 "Question: Did you have any consulting
09:29:37 agreement with Shire after you left?

09:29:40 "Answer: No.

09:29:40 "Question: What have you been doing since October 2008 -- professionally?

09:29:44 "Answer: I am consulting and I am a board member of some boards and I invest into companies myself, and I advise several venture capital groups, especially TVM (Techno Venture Management) in Munich, who had 1.4 billion in life science, and they have offices in Munich, Montreal and Singapore and Dubai.

09:29:48 09:29:50 09:29:53 09:29:58 09:30:06 09:30:12

09:30:17 "Question: What was your title at Jerini?

09:30:26 "Answer: Head of research and CSO (Chief Scientific Officer).

09:30:31

09:30:33 "Question: What is your current title?

09:30:35 "Answer: I'm self-employed, one man show.

09:30:44 "Question: And did your work on renin inhibitors involve the use of synthetic amino acids?

09:30:52

"Answer: Yes.

09:30:57 "Question: And just so --

09:30:58 "Answer: And one thing I can tell you is that we started traditional this group was very heavily relying on synthesis in solution for the peptides and that seemed so outdated to me that I said that we need to change there and go to solid phase synthesis, but since there were traditionally used very harsh conditions to release the peptides from the resin, we started a new investigation of

09:31:00 09:31:04 09:31:10 09:31:13 09:31:19 09:31:25

09:31:36 **linker, how to attach the peptide and release it on less**
09:31:41 **harsh conditions with only a few percent of trifluoric**
09:31:53 **acetic acid and to remove, to take use of a base labile**
09:32:00 **protecting group and this was an effort which we also**
09:32:02 **finally when a new machine came from Applied Biosystem a**
09:32:06 **peptide synthesizer. We were the ones actually rewriting**
09:32:10 **the whole machine and the cycles and reprogramming it,**
09:32:18 **adapting it to this new chemistry, and I implemented that**
09:32:23 **also in our research center in Japan when I worked in Japan,**
09:32:28 **the Hoechst research center.**
09:32:30 **"Question: Just to make sure I understand that**
09:32:34 **when you arrived and you started your work in the peptide**
09:32:40 **group, they were using solution-based synthesis?**
09:32:45 **"Answer: Yes.**
09:32:48 **"Question: And you thought that the way to**
09:32:50 **go would be to follow the solid phase synthesis route,**
09:32:54 **right?**
"Answer: Yes.
09:32:55 **"Question: And that had been revised in the**
09:33:00 **derived in the late 60s by Merrifield and his group, right?**
09:33:00 **"Answer: Yes.**
09:33:01 **"Question: And one of the things that you did**
09:33:03 **was that you looked at linkers that used less harsh**
09:33:06 **conditions that could release the molecule from the resin**
09:33:10 **more gently?**

09:33:11 "Answer: Yes. More gentle, and sometimes we
09:33:13 could choose which protected groups would stay on the
09:33:18 protecting amino acids, could be manipulated later on, and
09:33:22 they were very selective.
09:33:24 "Question: Fmoc is a linker molecule; is that
09:33:28 right?
09:33:29 "Answer: No, that's a protecting group.
09:33:31 "Question: Protecting group. Okay. What's the
09:33:33 purpose of that Fmoc protecting group?
09:33:36 "Answer: That's, you know, that couplings have
09:33:38 always the same pathway. It's activating of the amino acid
09:33:42 and adding it to the growing amino acid chain in the solid
09:33:47 phase, and then during that time you need one of the many
09:33:53 protecting groups which are available in peptide chemistry,
09:33:56 and then release it.
09:33:58 "Question: Did you have any responsibilities
09:34:01 related to pharmacology?
09:34:05 "Answer: No. I interacted -- they were
09:34:09 colleagues. We worked together because, of course, we
09:34:15 exchanged data. We were eager to get results.
09:34:18 "Question: Who was in charge of the
09:34:22 pharmacology group at that time?
09:34:24 "Answer: Afterwards it was Scholkens, but the
09:34:30 name before it escapes me.
09:34:35 "Question: At some point it became Dr.

09:34:40 **Scholkens?**

"Answer: Yes.

09:34:41 **"Question: Okay. Thank you. D-Tic, is that a**
09:34:44 **proline analog?**

09:34:47 **"Answer: D-Tic is, you can say -- you, in some**
09:34:51 **way, or you can also say it's a phenylalanine analog,**
09:34:59 **whatever. It's...**

09:35:03 **"Question: It just varies from phenylalanine by**
09:35:06 **one carbon, right?**

09:35:08 **"Answer: It varies by one carbon and it's**
09:35:11 **cyclized, yes.**

09:35:13 **"Question: When did you first begin to work on**
09:35:16 **any bradykinin-related product?**

09:35:21 **"Answer: I don't recall it anymore.**

09:35:22 **"Question: Approximately?**

09:35:24 **"Answer: Maybe we -- around 87/88 we may have**
09:35:28 **discussed that.**

09:35:29 **"Question: And what was your first task related**
09:35:45 **to a bradykinin project?**

09:35:50 **"Answer: I assigned the capacities within the**
09:35:57 **group and how we would go on this project. I assigned**
09:36:03 **Stephan Henke as the project leader.**

09:36:07 **"Question: Did you make any other assignments?**

09:36:10 **"Answer: No. That was not the way. Stephan**
09:36:15 **Henke was the project leader and that's it.**

09:36:18 "Question: And what was the project that you
09:36:21 started in 1987/1988 time frame?
09:36:26 "Answer: We tried to come up with a bradykinin
09:36:29 antagonist which would be -- would have sufficient
09:36:35 properties to investigate the contribution of bradykinin in
09:36:40 different pathophysiologies.
09:36:53 "Question: When you first started working on
09:36:55 the bradykinin antagonist project, were you intending to
09:36:58 develop a bradykinin antagonist as a pharmaceutical product?
09:37:02 "Answer: No.
09:37:02 "Question: When did it become part of the
09:37:10 effort of the bradykinin program to develop a bradykinin
09:37:13 antagonist as a pharmaceutical product?
09:37:19 "Answer: When we had identified what was later
09:37:22 on become icatibant Firazyr as a potential compound, which
09:37:32 would have sufficient drug-like properties.
09:37:36 "Question: You mentioned that you assigned
09:37:39 Stephan Henke as the project leader?
"Answer: Yes.
09:37:43 "Question: What was your role in the bradykinin
09:37:45 antagonist project when it began in 1987/1988?
09:37:52 "Answer: What we did, we designed, we chopped
09:37:57 up the molecule into different areas, so different
09:38:00 laboratories got assigned different areas. I took what was
09:38:05 the leftover, the C-terminal part, because no one expected

09:38:10 there to have potency or any beneficial effects, so I said I
09:38:15 would do that.
09:38:16 "Question: When you say you took the C-terminal
09:38:25 part, what do you mean by that?
09:38:27 "Answer: I mean to do medicinal chemistry work
09:38:35 SAR to see how this part of the molecule would interact with
09:38:39 the target.
09:38:39 "Question: When you began working on bradykinin
09:38:46 antagonists, were you aware of any literature or
09:38:50 presentations that were available explaining what was known
09:38:58 about bradykinin antagonists?
09:39:02 "Answer: There was a whole area of literature
09:39:03 at that time about different peptidic antagonists and
09:39:09 agonists and so on and B1 and B2 antagonists and mixtures of
09:39:15 those, mainly from academic labs.
09:39:19 "Question: Did you review that literature when
09:39:21 you began working on the project?
09:39:24 "Answer: Yes. I didn't do it personally, but
09:39:26 the project leader had to do that.
09:39:28 "Question: Did the project leader make a
09:39:30 presentation to you about what was in the literature?
09:39:35 "Answer: I don't recall any more, but most
09:39:38 likely, we looked at the data, say, because there were
09:39:41 discussions if it what was active for B1 receptor, what was
09:39:48 active for B2 receptor.

09:39:49 "Question: You mentioned some academic
09:39:54 institutions that had published on bradykinin and bradykinin
09:39:57 antagonists?
"Answer: Yes.
09:40:01 "Question: Do you recall what institutions had
09:40:03 published in that regard?
09:40:05 "Answer: I don't know any more, really, because
09:40:06 they were -- as I said, there were this South American, Sao
09:40:17 Paolo group. There was a very active group in Sherbrooke in
09:40:24 Canada. Regoli, I believe his name was Regoli. There were
09:40:31 some works done in Europe, in Sweden. I don't know any more
09:40:34 the academic liaison of that. So there were many. Stewart,
09:40:38 of course, and others.
09:40:40 "Question: In 1987 or 1988, when the BK
09:40:43 antagonist program began at Hoechst, were you aware of the
09:40:53 work by Dr. Regoli in Canada on BK antagonists?
09:41:01 "Answer: Sure.
09:41:02 "Question: Were you aware of the work by Dr.
09:41:08 Stewart and his colleagues in Colorado?
09:41:11 "Answer: Yes, I was aware.
09:41:12 "Question: You said that you assigned Dr. Henke
09:41:15 to be the project leader; correct?
"Answer: Yes.
09:41:19 "Question: In addition to yourself and Dr.
09:41:21 Henke, how many other people were working on developing BK

09:41:26 antagonists?

09:41:27 "Answer: I think -- I don't recall it
09:41:29 completely. Breiphol for sure was involved, Briephol, and
09:41:41 then I'm sure another chemist, maybe Dr. Koenig.

09:41:45 "Question: So maybe four people?

09:41:57 "Answer: Four laboratory heads, which always
09:42:05 translated into several more heads.

09:42:08 "Question: I see, including technicians, it
09:42:16 would have been a bigger group?

"Answer: Yes.

09:42:18 "Question: Did you and your group, this BK
09:42:20 antagonist group, did you get together on a regular basis to
09:42:24 discuss the research?

09:42:26 "Answer: Yes, we would discuss the research in
09:42:27 regular meetings.

09:42:28 "Question: How did you communicate with one
09:42:30 another about what was going on in the project?

09:42:33 "Answer: The process was we would submit
09:42:35 compounds and register them into the Hoechst library and
09:42:41 then we would get back depending on the capacity in the
09:42:44 pharmacology some results. And then we would look at these
09:42:49 results if there was anything going on, indicative of what
09:42:56 we wanted.

09:42:58 "Question: Have you ever heard of the guinea
09:43:11 pig pulmonary artery test?

09:43:17 "Answer: Sure.

09:43:17 "Question: Was that being done, do you recall?

09:43:20 "Answer: I think so, yes.

09:43:21 "Question: Who at Hoechst was doing that test?

09:43:23 "Answer: A technician -- first a technician in Dr. Scholkens' lab, and then later on Klaus Wirth, I believe, I believe. But he was the pharmacologist assigned.

09:43:38 "Question: Did you have any input into what pharmacological tests were being selected to test the molecules you were making?

09:43:45 "Answer: We had discussions with the pharmacologist and we would discuss what one could do to profile the compounds once they had reached a certain interest. If it would be done more, then the normal aorta strip test.

09:44:30 "Question: Do you recall what if anything was known about what changes had to be made to the sequence of bradykinin in order to make a bradykinin antagonist when you started the project?

09:44:49 "Answer: No, we started de novo, which can be also seen at the compounds registered, we explored the whole molecule for one lab explored the N-terminus, the middle, which was the hottest topic at that time, our expectations, and the C-terminus part.

09:45:11 "Question: When you say the C-terminus part,

09:45:13 **how many amino acids are you talking about?**

09:45:16 **"Answer: Around 4, I guess, if I recall right.**

09:45:18 **"Question: Was there an understanding that if**

09:45:30 **you substituted D-Phe at the 7 position that you would**

09:45:36 **achieve antagonism?**

09:45:38 **"Answer: There was the Stewart antagonist and**

09:45:42 **there were Regoli compounds around with D analogs, there**

09:45:50 **were Swedish patents with D analogs, so there were some, but**

09:45:54 **none of them were really potent.**

09:45:56 **"Question: What problems did you see that**

09:46:00 **needed to be addressed in terms of developing a bradykinin**

09:46:06 **antagonist when you began?**

09:46:10 **"Answer: At that time our understanding was**

09:46:12 **rudimentary, so we had to look if we would really hit the B2**

09:46:18 **receptor and not the B1 receptor. That was number one,**

09:46:23 **because there were reports all over that you hit both.**

09:46:27 **Second, that you don't have strong agonism remaining in your**

09:46:35 **molecule. Last, not least, achieving a potency which would**

09:46:40 **make it useful as a tool or a therapeutic indication.**

09:46:45 **"Question: And when you began the project in**

09:46:48 **1987, what was known about how to create a molecule that**

09:46:58 **would have B2 receptor effect and not B1 receptor effect?**

09:47:04 **"Answer: I don't recall it anymore, but it was**

09:47:07 **totally unclear and it was still maintained unclear up to**

09:47:12 **the years 2000 and later even.**

Depo readings.

09:47:15 **"Question: And what was known about how to**
09:47:18 **achieve a molecule that would avoid having a continued**
09:47:24 **strong agonistic effect?**
09:47:30 **"Answer: At that time we couldn't screen, we**
09:47:33 **couldn't predict in any way agonism. That would have to be**
09:47:41 **worked out in different pharmacological assays.**
09:47:50 **"Question: You mentioned another goal was to**
09:47:53 **achieve increased potency. Correct?**
09:47:59 **"Answer: Correct, yes.**
09:48:00 **"Question: And what do you mean when you say**
09:48:04 **potency, what do you have in mind?**
09:48:07 **"Answer: You have in mind that you can compete**
09:48:13 **with the endogenous substrate, bradykinin in this case, and**
09:48:23 **therefore you have to know first also how much bradykinin is**
09:48:29 **circulating, and second that your compound can really**
09:48:33 **compete there to displace the circulating natural substrate.**
09:48:42 **"Question: In order to complete with the**
09:48:45 **natural substrate, the antagonist has to bind to the**
09:48:52 **receptor with some avidity; correct?**
09:48:57 **"Answer: Yes, to the GPCR. So normally**
09:49:01 **teaching in med chem as you should be, around ten nanomolar,**
09:49:05 **between 10 to 15 nanomolar may work, but better below ten**
09:49:13 **nanomolars.**
09:49:14 **"Question: If you could turn to Page 438 of**
09:49:17 **that document, there's.**

Depo readings.

"Answer: 38, yes.

09:49:25 **"Question: There is a list of potential**

09:49:29 **applications of a bradykinin antagonist listed one through**

09:49:33 **six, correct?**

09:49:36 **"Answer: Yes.**

09:49:36 **"Question: No. 3 includes edemae, right?**

09:49:46 **"Answer: Yes.**

09:49:47 **"Question: Do you know what that means? What's**

09:49:51 **included in the word edemae on that page, do you know?**

09:49:56 **"Answer: I recall that scientifically it was**

09:50:00 **discussed that the endothelial layer leaking, that's all I**

09:50:09 **recall and then extravasation of fluid.**

09:50:14 **"Question: You wouldn't have known about**

09:50:18 **hereditary angio edema?**

"Answer: Not at this time.

09:50:21 **"Question: Why not?**

09:50:21 **"Answer: Because it was not early on linked to**

09:50:32 **that. I don't recall in detail but I think we looked at**

09:50:41 **hereditary angio edema, when we had HOE140 in our hands.**

09:50:44 **Much later.**

09:50:44 **"Question: But at least at this point in**

09:50:46 **time --**

09:50:48 **"Answer: It's a typical inflammatory indication**

09:50:52 **that you have edema, inflammatory reaction, that you have**

09:50:55 **edema.**

Depo readings.

09:50:57 **"Question: I'm am going to ask the court**
09:50:59 **reporter to mark as the next exhibit Knolle 3 a document**
09:51:03 **with production numbers SHRSAN 00395334 through 3956385, the**
09:51:12 **cover of the document, again, appears to be the spine of a**
09:51:19 **binder. The binder is entitled HOE140. Dr. Knolle, I know**
09:51:24 **that's another big document I am handing you there. I guess**
09:51:27 **the first question is, do you recognize the binder that's**
09:51:30 **copied on the cover?**
09:51:32 **"Answer: No.**
09:51:32 **"Question: What does the German language**
09:51:36 **underneath HOE140 say?**
09:51:40 **"Answer: Protocols of the routine meeting**
09:51:50 **HOE140 2.0. It looks like development.**
09:51:55 **"Question: Protocols of the routine meeting**
09:51:57 **HOE140 2.0?**
09:52:02 **"Answer: I don't know what 2.0 has to do here.**
Industry for zero...
09:52:10 **"Question: Do you understand what protocols of**
09:52:13 **the routine meeting means?**
09:52:15 **"Answer: Yes, I understand that these are the**
09:52:17 **protocols which were generated during the development of a**
09:52:25 **compound and you were invited or not invited, depending on**
09:52:34 **the subject of this; if it needs chemistry or support of**
09:52:42 **chemistry, or something like that pilot plant, then you were**
09:52:47 **invited.**

Depo readings.

09:52:47 **"Question: Okay. You can feel free to look at**
09:52:50 **any part of that document that you want to but I would like**
09:52:52 **to direct you to the page that ends with 395678. Very close**
09:53:03 **to the back of the document, I think. Do you have that?**
09:53:10 **"Answer: 680?**
09:53:12 **"Mr. Haug: 678.**
09:53:12 **"Question: 678. This is a document that is**
09:53:20 **dated the first of December 1988; correct?**
09:53:22 **"Answer: It's dated, yes, okay, but the meeting**
09:53:29 **took place 24th of November.**
09:53:36 **"Question: In the middle there, Part 3, it says**
09:53:39 **the third meeting of the project team bradykinin antagonists**
09:53:44 **on November 24th, 1988; right?**
09:53:49 **"Answer: Yes.**
09:53:50 **"Question: And then in the upper left-hand**
09:53:53 **corner it says 'Dr. S. Henke Pharma Synthese'?**
09:53:58 **"Answer: That's the medicinal chemistry.**
09:54:03 Q. **That's the medicinal chemistry, what, department?**
09:54:08 **"Answer: Yes.**
09:54:09 **"Question: Somebody has dated it December 6,**
09:54:13 **1988 in the upper right-hand corner by hand, right?**
09:54:17 **"Answer: That's most likely when it was filed,**
09:54:20 **I guess.**
09:54:22 **"Question: It says that the participants here**
09:54:30 **there were several of them including yourself. Right?**

Depo readings.

09:54:35 "Answer: Yes.

09:54:35 "Question: And from chemistry it was yourself, Dr. Henke and Dr. Breipohl, right?

09:54:40 "Answer: Yes.

09:54:43 "Question: I'm going to mark as Knolle Exhibit 4 a multi-page document with production numbers SHRSAN00382912 through 383302. The cover of this document has a number on it, '24391.'

09:54:45 "Dr. Knolle, would you just take a moment and look through that document and tell me if you recognize what that is?

09:54:50 "Answer: This looks like all laboratory notebooks.

09:54:58 "Question: Can you tell whose laboratory notebook this is?

09:55:13 "Answer: No. Could be someone from the technicians, I would guess. For sure it's not my handwriting. It's some of the technicians most likely.

09:55:17 "Question: Okay. If you look at Page 913, which is the back of the cover -- one more back.

09:55:20 "Answer: It says Henke, Stephan.

09:55:23 "Question: If you look at that page, it has Dr. Henke's name at the top, correct?

09:55:23 "Answer: Yes.

09:55:26 "Question: And then if you look at the next

09:55:26

09:55:29

09:55:30

09:55:32

09:55:42

09:55:46

09:55:48

09:56:00

09:56:04

09:56:05

09:56:06

09:56:09 page -- I'm sorry, two pages over, 915?
09:56:17 "Answer: 915 -- I have 914 and 916.
09:56:20 "Question: I think you have got this one
09:56:22 flipped over, where it says 'Redacted.' Flip that one over.
09:56:25 That's 915?
09:56:27 "Answer: Okay. Yes.
09:56:27 "Question: Does it indicate there whose
09:56:30 laboratory notebook this is.
09:56:32 "Answer: Yes, Stephan.
09:56:34 "Question: You mean Dr. Henke?
09:56:36 "Answer: Yes.
09:56:36 "Question: So this notebook, Dr. Henke's
09:56:40 notebook of someone you were supervising, right?
09:56:43 "Answer: I supervised Henke. It was Henke's
09:56:45 responsibility to make his lab work, perform.
09:56:49 "Question: If you turn to Page 382961?
09:56:56 "Answer: 383?
09:56:57 "Question: 382961, it's actually page 35 of the
09:57:03 laboratory notebook.
09:57:06 "Answer: Okay.
09:57:06 "Question: Then there is a structure there that
09:57:11 is Arg-Arg-Hyp-Pro-Gly-Thi-Ser-D-Tic Thi Arg hydroxy; right?
09:57:27 "Answer: Yes.
09:57:27 "Question: I'm sorry. Again, that was D-Arg at
09:57:31 the beginning. I left that off.

Depo readings.

"Answer: Yeah.

"Question: And here instead of D-Phe at the 7 position this has D-Tic, right?

"Answer: Yes.

"Question: It was your portion of the molecule that included the D-Tic for D-Phe substitution. Right?

"Answer: Yes.

"Question: And can you tell me why you made that substitution?

"Answer: Yes, I can tell you. As you know, there are many, many analogs of unnatural amino acids with different properties as, for example, provided by Stewart in his talk on the N-termini most likely and this didn't seem to me very useful so I wanted to -- didn't go to substituted aromatic rings or introducing halogens or other things which I thought, if you want to do something there, you have to do something more drastically. You have to think about conformational restriction to generate a compound which has a preferred conformation to interact with the target.

"Question: The conformational restriction was provided by the D-Tic, correct?

"Answer: Yes, it was a start of the conformational restriction because you saw the other papers you gave me, it was just a slight increase in potency. So obviously this D-Tic analog was not sufficient to provide

09:59:20 **conformational restriction, as shown in the other things you**
09:59:25 **showed me.**
09:59:25 **"Question: So the change from bradykinin to**
09:59:33 **D-Phe 7 bradykinin in your opinion wasn't a large enough**
09:59:37 **improvement in efficacy, right?**
09:59:41 **"Answer: No, ten to the minus 6 is not high**
09:59:47 **potency, in pharmaceutical compounds, I wouldn't have**
09:59:49 **licensed that.**
09:59:50 **"Question: So you wanted to change at the 7**
09:59:53 **position -- you wanted to provide an additional change at**
09:59:56 **the 7 position to make some structural rigidity there,**
10:00:00 **correct?**
10:00:01 **"Answer: I wanted to provide there a new thing**
10:00:05 **the others didn't think about, and this is structural**
10:00:09 **restriction, as you do normally because you gain entropy**
10:00:16 **terms of binding. This is a common game in medicinal**
10:00:21 **chemistry that you try to find how to tweak the molecules in**
10:00:24 **such a way that you can get into the interaction with an**
10:00:32 **already preferred conformation to garner this entropic**
factor.
10:00:35 **"Question: In your answer you referred to 'this**
10:00:37 **analog here.' Are you talking about this compound that's**
10:00:41 **shown on Page 961?**
10:00:48 **"Answer: Yes, yes. So I don't know, you have**
10:00:51 **to look it up, but it says it's S 88 1619 is the**

10:00:57 **registration number, because I took over at the C-terminus**
10:01:02 **because everyone expected exchanges in other region to be**
10:01:08 **beneficial.**
10:01:08 **"Question: Could you turn to the Page 980, ends**
10:01:13 **with 980?**
10:01:16 **"Answer: 382?**
10:01:18 **"Question: 382980, yes. Do you have that?**
10:01:22 **"Answer: Yes.**
10:01:22 **"Question: I just want to know what that**
10:01:26 **peptide structure is, to the extent you know?**
10:01:32 **"Answer: I don't recall that. I don't know**
that anymore.
10:01:43 **"Question: Okay.**
10:01:44 **"Answer: And it doesn't say the operator, but**
10:01:51 **must have been interesting too because it's 200 mg, but for**
10:01:57 **what project I don't recall, or if he used it also in the**
10:02:05 **bradykinin. I don't know. I don't know.**
10:02:05 **"Question: Could you turn to Page 383063?**
10:02:11 **"Answer: 383?**
10:02:13 **"Question: 063.**
10:02:17 **"Answer: Yes.**
10:02:17 **"Question: And on this page there's an entry --**
10:02:25 **strike that.**
10:02:26 **"Can you tell me what date that is on 063?**
10:02:33 **"Answer: Let's see if I can see this. Not**

10:02:38 **really, its again seems to be Burow as an operator and I**
10:02:44 **can't read his handwriting. Somewhere in September. '88.**
10:02:49 **"Question: Okay, September '88. And in this**
10:02:52 **September '88 work, there is a structure provided on '063,**
10:03:01 **correct?**
10:03:03 **"Answer: On 063, yes.**
10:03:05 **"Question: And in this instance in September**
10:03:10 **'88, it's D-Tic at the 7 position, pro at the 8 position,**
10:03:19 **right?**
10:03:19 **"Answer: Yes.**
10:03:19 **"Question: So at this point, you're still using**
10:03:24 **a natural amino acid at the 8 position, right?**
10:03:29 **"Answer: The proline, yes. But what is here**
10:03:34 **interesting is that we used instead of the arginine here a**
10:03:41 **phenylalanine and I think that was the driving force for**
10:03:47 **this derivative.**
10:03:47 **"Question: Right. Sorry, in that regard, if**
10:03:52 **you would just turn back a few more pages, which I think is**
10:03:56 **still in September of '88, to 383058?**
10:04:02 **"Answer: 58, yes.**
10:04:03 **"Question: Do you see there's a structure at**
10:04:10 **the top of that page?**
10:04:13 **"Answer: Yes. And there we have D-Tic Arg**
C-Terminal, yes.
10:04:17 **"Question: So there you have maintained the Arg**

10:04:20 **in the 9 position, right?**

10:04:21 **"Answer: Yes.**

10:04:23 **"Question: But then, in October of '88, if you**

10:04:28 **turn to Page 383074, there is a structure provided on Page**

10:04:36 **68 of the laboratory notebook there, on October 25th, 1988,**

10:04:40 **right?**

"Answer: Mm-hmm.

"Question: And here you have changed the pro at

the 8 position AOC, Right?

"Question: To the synthetic amino acid;

correct?

"Answer: But the interesting thing here is the

10:04:42 **compound was not active.**

10:04:42 **The interesting thing is the beta alanine there,**

10:05:17 **R, because this was never a potent compound I believe.**

10:05:22 **"Question: Sorry the beta alanine?**

10:05:25 **"Answer: Yes. It says T-serine beta-alanine I**

10:05:29 **read it, or beta Phe, D-Tic AOC Arg.**

10:05:33 **"Question: I'm sorry. Just so we're on the**

10:05:37 **same page. We're talking about the 6 position now, right?**

10:05:40 **"Answer: Yes.**

10:05:41 **"Question: What do you read that to say at the**

10:05:43 **6 position?**

10:05:44 **"Answer: I think it's either beta Phe or beta**

10:05:50 **ala -- it's beta alanine.**

Depo readings.

10:05:50 "Question: What is beta alanine?

10:05:53 "Answer: There you shift the amino group one position further, it's breaking up the potential conformation because it's much more flexible and I guess this alone did not provide enough, so I think this derivative, despite having D-Tic AOC Arg, was never potent. So this is not sufficient. It just shows the ensemble of the conformation which will provide you with the potency. That's why the beta ala here was most likely introduced.

10:06:40 "Question: If you turn to Page 383081?

10:06:46 "Answer: 3830 --

10:06:48 "Question: 81, you see in that very same time frame, I think it's 10/28/88 but it's hard to work out the dates because of the way these are copied?

10:07:05 "Answer: Yes.

10:07:06 "Question: You see there that you created a structure that doesn't have the beta-alanine at the 6 position. Correct?

10:07:15 "Answer: Correct.

10:07:15 "Question: It has glyc?

10:07:18 "Answer: Glycine, yes.

10:07:18 "Question: And then the D-Tic and then the AOC. Right?

10:07:23 "Answer: Yes.

10:07:24 "Question: Dr. Knolle, earlier you indicated

10:07:26 **that when the peptide side process or the peptide effort to**
10:07:34 **make a BK antagonist started, that you were using solution**
10:07:39 **phase synthesis. Is that right?**
10:07:41 **"Answer: Partially for larger quantities, yes,**
10:07:46 **and for smaller quantities we used solid phase synthesis,**
10:07:51 **yes.**
10:07:51 **"Question: Solid phase synthesis was known in**
10:07:57 **1988 when you started the project, right?**
10:08:01 **"Answer: Sure, yes.**
10:08:02 **"Question: And were there machines available**
10:08:05 **for doing peptide synthesis in 1988?**
10:08:09 **"Answer: Yes. As I said, we adopted the**
10:08:12 **Applied Biosystems to our chemistry.**
10:08:16 **"Question: Did you ever go out to Applied**
10:08:19 **Biosystems and learn how to use their machine?**
10:08:21 **"Answer: No, they would come to us, an engineer**
10:08:25 **from San Francisco and chemist. But they were interested to**
10:08:29 **take our protocols on their machine because it was a total**
10:08:36 **different chemistry and allowed more sensitive things.**
10:08:40 **"Question: When you do solid phase synthesis of**
10:08:43 **a peptide like a bradykinin antagonist you start with an**
10:08:47 **amino acid that's attached to a resin by the carboxy group,**
10:08:57 **right?**
10:08:57 **"Answer: Yes, to a linker first and then to the**
10:09:00 **resin.**

Depo readings.

10:09:03 **"First the carboxylic acid of the first amino**
10:09:07 **acid is linked to what is called linker, which is a**
10:09:11 **permanent link, then linked to the polymer which is used**
10:09:18 **"Question: Just so it's clear, the polymer that**
10:09:21 **you are referring to is the solid phase resin. Right?**
10:09:26 **"Answer: Resin, yes.**
10:09:27 **"Question: And then there's a linker that's**
10:09:31 **permanently linked to that resin, right?**
10:09:33 **"Answer: Yes.**
10:09:33 **"Question: And then the carboxylic acid end of**
10:09:37 **the amino acid is linked to that linker, right?**
10:09:40 **"Answer: Yes.**
10:09:40 **"Question: And the other end of the amino acid**
10:09:43 **that is linked now to the resin has an amino group on it.**
10:09:47 **Right?**
10:09:48 **"Answer: One of them as a protected amino group**
10:09:52 **on it.**
10:09:53 **"Question: It may also have some group on the**
10:09:55 **side chain that needs protection, right?**
10:09:58 **"Answer: Yes.**
10:09:58 **"Question: But it has at least an amino group**
10:10:01 **that needs to be protected?**
10:10:02 **"Answer: Yes.**
10:10:02 **"Question: And there were protecting groups**
10:10:05 **that were known in the art for protecting that amino group,**

10:10:13 **right?**

10:10:14 **"Answer: Sure, there are many, many, many out**

10:10:18 **there.**

10:10:19 **"Question: And there are protecting groups that**

10:10:21 **were known for protecting the side chains as well, right?**

10:10:24 **"Answer: Many, yes.**

10:10:25 **"Question: Now, the amino acids were added by**

10:10:36 **reacting the carboxylic acid end of the next amino acid to**

10:10:40 **the amino group of the attached amino acid, right?**

10:10:44 **"Answer: Yes.**

10:10:45 **"Question: In order to do that you have to**

10:10:47 **remove the protecting group on the attached amino acid,**

10:10:51 **right?**

10:10:53 **"Answer: Um-hmm.**

10:10:53 **"Question: And what reagent do you use to**

10:10:56 **remove that protecting group on the attached amino acid in**

10:11:00 **order to join, or link the next amino acid?**

10:11:03 **"Answer: We used in most case some bases,**

10:11:07 **different type of bases. In most of the cases, sometimes**

10:11:11 **not, also some acid labile, depending on the problem of the**

10:11:18 **peptide sequence.**

10:11:23 **"Question: The protecting group that you used**

10:11:25 **to protect the amino acid -- the amino end of the amino**

10:11:33 **acid -- was Fmoc, right?**

10:11:35 **"Answer: In the majority of cases, yes.**

Depo readings.

10:11:37 "Question: And Fmoc is base labile, meaning you
10:11:40 can remove it with a base, right?
10:11:42 "Answer: Yes.
10:11:43 "Question: And the base that you used most
10:11:44 commonly was piperidine, right?
10:11:47 "Answer: Yes.
10:11:47 "Question: And you do removing the protecting
10:11:52 group on the amino acid, bonding the next carboxylic acid of
10:11:56 the sequential amino acid, you do it in sequential fashion
10:11:59 until you have the amino acid sequence that you are seeking,
10:12:04 right?
10:12:04 "Answer: Yes, hopefully.
10:12:06 "Question: And then if you are using Fmoc, for
10:12:12 example, to protect the amino acids as they are added, then
10:12:16 you have your amino acid sequence with the resin attached at
10:12:20 one end and the Fmoc at the other end, right?
10:12:24 "Answer: At the end of the synthesis you remove
10:12:27 the N-terminal amino protecting group as well and then you
10:12:34 cleave it and then you release it. That's how it's done.
10:12:37 "Question: And in that answer when you say 'At
10:12:41 the end of the synthesis you remove the N-terminal amino
10:12:47 protecting group,' you meant you remove the Fmoc, right?
10:12:53 "Answer: Always, yes.
10:12:53 "Question: And all of that was known in 1988?
10:12:57 "Answer: The solid phase synthesis and the use

10:13:01 **of different protecting groups was known in the -- however,**
10:13:04 **each laboratory developed preferred procedures, procedures,**
10:13:13 **minor changes or major changes.**
10:13:15 **"Question: But the general scheme that you and**
10:13:17 **I just discussed, that was known in 1988?**
10:13:20 **"Answer: Yes, yes, yes.**
10:13:23 **"Question: I'm going to ask the court reporter**
10:13:24 **to mark as the next exhibit Knolle 5, the '333 patent, which**
10:13:30 **is the patent in suit in this case. This particular copy**
10:13:33 **has production numbers SHRSAN0043622 through 433650.**
10:13:47 **"Dr. Knolle, can you just take a minute or two**
10:13:50 **and flip through Knolle 5 and tell me if you have seen this**
10:13:55 **before?**
10:14:00 **"Answer: I assume that I have seen that before**
10:14:06 **from my old ages. Sure, it was from my department, yes.**
10:14:11 **"Question: Do you recognize this to be the**
10:14:14 **'333 patent?**
10:14:17 **"Answer: I recognize this to be the patent**
10:14:20 **where we, I believe, enclosed 140, its development candidate**
is described in here. I don't know but I think.
10:14:32 **"Question: You believe that this is the patent**
10:14:33 **that describes the development of HOE140. Is that what you**
10:14:36 **said?**
10:14:37 **"Answer: Yes, I think so. It should be part of**
10:14:41 **this application, but I'm not sure, because so many patents,**

10:14:50 so long ago.

10:14:52 "Question: If you look at what I am going to
10:14:54 call the first page, even though it's not actually the first
10:14:57 page of that exhibit, if you flip that over, on the back of
10:15:00 the first page, that is the cover of the patent. Do you see
10:15:05 in the upper right-hand corner the No. 5,648,333?

10:15:10 "Answer: '333, yes.

10:15:11 "Question: And do you see your name listed
10:15:13 amongst the inventors?

10:15:18 "Answer: I assume. Yes. There it is, yes.

10:15:20 "Question: I have sort of a limited number of
10:15:26 things that I would like to ask you about in here.

10:15:32 If you could turn to Page -- to Column 12. If
10:15:37 you look at the top of each page, you will see column
10:15:41 numbers?

10:15:47 "Answer: Okay.

10:15:48 "Question: And about halfway down on Column 12,
10:15:52 at Line 27, do you see it says, The most preferred peptide
10:15:59 of the Formula 1 is
10:16:07 H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH?

10:16:13 "Answer: Yes.

10:16:14 "Question: That is the structure of icatibant.
10:16:18 Correct?

10:16:19 "Answer: Yes, correct.

10:16:20 "Question: Just underneath that it says, 'The

10:16:23 **invention furthermore relates to a process for the**
10:16:25 **preparation of the peptides of the Formula 1, which**
10:16:28 **comprises (a)reacting a fragment having a C-terminus free**
10:16:35 **carboxyl group or its activated derivative with an**
10:16:38 **appropriate fragment having an N-terminal free amino group**
10:16:43 **or (b) synthesizing the peptide step-wise, optimally**
10:16:49 **splitting off one or more protective groups temporarily**
10:16:52 **introduced for the protection of other functions in the**
10:16:55 **compound obtained according to (a) or (b) and optimally**
10:17:01 **converting the compounds of the Formula 1 thus obtained into**
10:17:04 **their physiological tolerable salt.**
10:17:08 **"Do you see that?**
10:17:09 **"Answer: Yes.**
10:17:09 **"Question: Can you explain what the difference**
10:17:11 **is between (a) and (b)?**
10:17:15 **"Answer: That's very clear that 1A refers to a**
10:17:18 **fragment and (b) refers to the solid phase step-wise**
10:17:27 **synthesis.**
10:17:27 **"Question: And (b) is the synthetic steps that**
10:17:30 **you and I just went through a few minutes ago together.**
10:17:34 **Right?**
"Answer: Yes.
10:17:35 **"Mr. Haug: Objection.**
10:17:35 **"Question: Now, it says that the protective**
10:17:40 **groups are temporarily introduced for the protection of**

10:17:44 other functions. Do you see that?

10:17:47 "Answer: Yes.

10:17:48 "Question: Why is it that the protecting groups

10:17:53 are temporarily introduced?

10:17:56 "Answer: To prevent side reactions, so that you

10:17:59 do couplings to other parts of the growing peptide chain,

10:18:07 for example, can be one reason. Or you want to manipulate a

10:18:14 certain side chain with a synthetic intervention later on,

10:18:21 so you selectively create a cluster of protecting groups

10:18:27 which will allow you the desired synthetic manipulations.

10:18:31 "Question: And it's a temporary introduction

10:18:35 because the protecting groups are put on in order to carry

10:18:40 out some chemistry and then they are taken off. Right?

10:18:43 "Answer: Yes, they are temporarily put on, or

10:18:46 even left there, depends all on the goal of your synthetic

10:18:54 analog that you have in mind.

10:18:55 "Question: When you went back to Jerini from

10:18:58 Axys, I think you already said this, but Jerini was a

10:19:02 company that had already been formed and was operating,

10:19:05 right?

10:19:05 "Answer: Yes. It was a small group of peptide

10:19:08 synthesis ongoing on paper for high throughput synthesis of

10:19:14 peptides displayed on paper membranes to investigate

10:19:20 immunological responses and stuff like that.

10:19:24 "Question: I'm sorry if I already ask you this,

10:19:27 **but was Jerini formed by your colleague?**

10:19:31 **"Answer: Yes, it was formed by Jens**

10:19:37 **Schneider-Mergener.**

10:19:39 **"Question: And when you went to Jerini, did he**

10:19:42 **contact you about coming there?**

10:19:44 **"Answer: Yes.**

10:19:44 **"Question: And how many people worked at Jerini**

10:19:47 **when you arrived?**

10:19:49 **"Answer: I don't know, 12, maybe 15 maximum.**

10:19:58 **"Question: You were the chief scientific**

10:19:59 **officer?**

10:20:00 **"Answer: Yes, also Jens was the CEO and we**

10:20:04 **wanted to go into drug discovery and development.**

10:20:07 **"Question: Did you work to raise funds for the**

10:20:10 **company?**

10:20:10 **"Answer: Yes, sure.**

10:20:15 **"Question: Can you tell me the kinds of things**

10:20:17 **you did in that regard?**

10:20:19 **"Answer: No, we went to investors and gave**

10:20:22 **presentations about the company and then to kick-start the**

10:20:25 **development of the company as a company, a research and**

10:20:28 **development company, we also considered to in-license the**

10:20:41 **product, I knew and saw that it had at least good safety and**

10:20:46 **still had to find its place in the therapeutic field.**

10:20:50 **"Question: You mean HOE140?**

Depo readings.

10:20:53 **"Answer: Yes, but as I said, we approached, I**
10:20:59 **believe it was Aventis at that time, and said if we could**
10:21:03 **get this compound.**
10:21:04 **"Question: What was their response?**
10:21:08 **"Answer: Their response was, 'Leave me alone.**
10:21:14 **It's a dead compound sitting in the basement of the peptide**
10:21:19 **pilot plant and why do you want to resurrect that asset?'**
10:21:27 **"So I insisted that we think that there might be**
10:21:32 **possibilities and the first indications we explored were**
10:21:35 **liver cirrhosis followed by hereditary angioedema.**
10:21:43 **"Question: You went to Aventis and they said,**
10:21:50 **'It's a dead compound, why are you interested in this?,'**
10:21:58 **right?**
10:21:59 **"Answer: Yes.**
10:21:59 **"Question: And then what did you say?**
10:22:01 **"Answer: I said, 'I want to explore therapeutic**
10:22:06 **applications,' and they said fine. And I went to the head**
10:22:10 **of business development, Hoffstaetter, and to Frank Douglas,**
10:22:14 **the board member for research and development, and asked if**
10:22:18 **we could get it for a decent price.**
10:22:23 **"Question: And did you?**
10:22:24 **"Answer: Yes, I was very happy with the deal.**
10:22:26 **"Question: Why were you happy with the deal?**
10:22:29 **"Answer: Because we inherited for free 6.2**
10:22:32 **kilograms of HOE140 for free from the pilot plant and it was**

10:22:36 **still stable after sitting many years there in the dark.**

10:22:39 **"Question: So Aventis --**

10:22:41 **"Answer: It's worth 6 million if you get it**

10:22:46 **synthesized by Bachem.**

10:22:48 **"Question: Aventis gave you 6 kilograms of**

10:22:51 **HOE140 as part of the deal?**

10:22:53 **"Answer: Yes, whatever was there we could get.**

10:22:55 **And then we did run in difficulties in the financing because**

10:22:59 **we ran out of money, basically. On the last four weeks we**

10:23:04 **ran on a credit line, and there was 9/11 and all the**

10:23:23 **investors stopped talking and then we made a deal in**

10:23:25 **October. That was very tight. That's the whole story.**

10:23:29 **"Question: That's the story of how you got the**

10:23:31 **license, right?**

10:23:37 **"Answer: The license and the financing, before**

10:23:41 **being bankrupt completely.**

10:23:42 **"Question: I'm going to mark as Knolle Exhibit**

10:23:46 **No. 6 a document with production numbers SHRSAN00286151**

10:24:03 **through 286195. It's a license agreement between Aventis**

10:24:10 **and Jerini. Just take a moment and look through that and**

10:24:14 **tell me if you have seen it before?**

10:24:16 **"Answer: Yes, I have seen it now.**

10:24:18 **"Question: Were you involved in negotiating**

10:24:20 **this license?**

10:24:23 **"Answer: I was negotiating the license solely.**

Depo readings.

10:24:26 "Question: Solely?

10:24:27 "Answer: Solely with a lawyer from Hengeler & Mueller in Frankfurt.

10:24:30 "Question: And this license is dated November the 1st, 2001. Correct?

10:24:31 "Answer: November 2001, yes.

10:24:34 "Question: It's at the top right under license agreement, November the 1st. Do you see that?

10:24:38 "Answer: Yes.

10:24:40 "Question: And if we look under the -- on the first page under the Whereas clauses, it says that the licensee, I am in the second paragraph, the licensee based on its expertise in peptidomimetics and their therapeutic applications has identified the potential of icatibant for treatment of the hepatorenal syndrome.

10:24:42 "Do you see that?

10:24:45 "Answer: Yes.

10:24:45 "Question: And if we look under the -- on the first page under the Whereas clauses, it says that the licensee, I am in the second paragraph, the licensee based on its expertise in peptidomimetics and their therapeutic applications has identified the potential of icatibant for treatment of the hepatorenal syndrome.

10:24:49 "Do you see that?

10:24:52 "Answer: Yes.

10:24:57 "Question: That's not the same as HAE. Right?

10:25:03 "Answer: No.

10:25:06 "Question: Can you explain why not, why it's not for HAE?

10:25:10 "Answer: Because this was written there because there was our first target, and that's the target we talked to the VCs about, and this hepatorenal syndrome was driven, mostly by liver cirrhosis. We did some studies, clinical

10:25:12 "Question: Solely?

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10:25:31 "Do you see that?

10:25:40 "Answer: Yes.

10:25:50 10:25:54 10:25:59 10:26:02 10:26:05 10:26:10 10:26:11 10:26:16 10:26:20 10:26:22 10:26:24 10:26:26 10:26:37 10:26:40 10:26:44 10:26:50 10:26:54 10:26:58 10:27:08 10:27:11 10:27:14 10:27:19 10:27:21 10:27:23

studies, and they were not successful because the baseline of these patients was so horrid and variable, so to prove an effect there was far beyond our reach. But we didn't know when we started it.

"Question: Okay. So the hepatorenal syndrome is just a part of people who have liver cirrhosis?

"Answer: Yes.

"Question: And then the licensor, Aventis, they kept osteoarthritis for themselves. Right?

"Answer: Yes.

"Question: And did you have an understanding at the time as to why that was?

"Answer: Yes. There was, Martin, I believe, a Martin and Schoelkens, I believe, was believing that arthritis could be an indication, and I apparently didn't believe in it. But that doesn't matter. So we, it was clear from the licensing strategy I had to be frankly because originally when I first went I got it for good, and it was a nice move of myself saying to them, 'You can still investigate osteoarthritis,' made good politics.

"Question: Were they -- they being Aventis -- were they planning to use icatibant for the treatment of osteoarthritis?

"Answer: Intraartricular and they went to a 2000 people study comparing icatibant injected

10:27:31 **intraarticularly into the knee joint versus steroids as a**
10:27:34 **comparator.**
10:27:34 **"Question: And it failed?**
10:27:37 **"Answer: It failed majorly yes.**
10:27:39 **"Question: Icatibant failed to show efficacy**
10:27:44 **against all the diseases it was tested against except for**
10:27:48 **HAE. Right?**
10:27:53 **"Answer: I wouldn't subscribe to that. It was**
10:27:55 **also investigated in asthma by Hoechst, who are HMR, and**
10:28:03 **there were some signs of activity but that was stopped.**
10:28:06 **"Question: On the same page under article 4**
10:28:10 **towards the bottom, you see milestones and royalties?**
10:28:14 **"Answer: Yes.**
10:28:14 **"Question: And then the milestones are listed,**
10:28:16 **and the first sub-listing there it says: 'LICENSEE shall**
10:28:22 **pay, following the signature of this Agreement, a signing**
10:28:26 **fee of 200,000 euros'?**
10:28:30 **"Answer: Yes.**
10:28:30 **"Question: Do you see that?**
10:28:32 **"Answer: Yes.**
10:28:32 **"Question: Did that occur?**
10:28:35 **"Answer: Sure. Otherwise, it wasn't -- we**
10:28:37 **wouldn't have gotten anything.**
10:28:39 **"Question: So you paid 200,000 euros on signing**
10:28:45 **day, Jerini did, for this product?**

Depo readings.

10:28:47 **"Answer: I guess so. Otherwise, we wouldn't have gotten it.**

10:28:49 **"Question: So Jerini obtained this product from Aventis to begin testing for 500,000 euros. Right?**

10:28:54 **"Answer: 200,000.**

10:29:00 **"Question: 200,000?**

10:29:02 **"Answer: To start up, yes, only after Phase IIb as it says here. We never made the Phase IIb.**

10:29:04 **"Question: You never made a Phase IIb?**

10:29:17 **"Answer: We went straight to Phase III, Orphan Drug.**

10:29:22 **"Question: I am sorry. I was just trying to make sure that in my next question I was accurately articulating what the assets were at Jerini when you sold yourselves to Shire.**

10:29:24 **"Answer: The major asset was Firazyr because it had the approval already in the E.U. under the central procedure and it was very clear that if you would repeat a little bit more patients and a little bit different calculation, adapted statistics better, adapted to small sized clinical trials, that the U.S. trial would be positive, too, because we saw that in the data already.**

10:29:24 **"Question: Dr. Knolle, do you know how much Shire paid for Jerini?**

10:29:36 **"Answer: Sure.**

10:29:40

10:29:46

10:29:50

10:29:59

10:30:03

10:30:09

10:30:13

10:30:16

10:30:18

Depo readings.

10:30:19 "Question: How much?

10:30:21 "Answer: I think, I don't recall it exactly,

10:30:24 560 million or so as it's published, you know."

10:30:34 THE COURT: Let's take a stretch.

10:30:36 (Recess taken.)

MR. WIESEN: Your Honor the defendants call Dr. Ronald Raines, and Mr. Stull will conduct the examination.

MR. STULL: Good morning, Your Honor. Coy Stull on behalf of Fresenius.

... RONALD RAINES, having been duly sworn as a witness, was examined and testified as follows ...

DIRECT EXAMINATION

MR. STULL: Good morning, Your Honor.

THE COURT: Good morning.

BY MR. STULL:

Q. Good morning, Dr. Raines. Could you state your full name for the record?

A. Ronald T. Raines.

Q. And where are you employed?

A. At the Massachusetts Institute of Technology.

Q. What is your position there?

A. I am a professor in the Department of Chemistry.

10:55:42 Q. And what are your responsibilities as a professor of

10:55:45 chemistry?

10:55:45 A. My responsibilities are to teach classes in biological

10:55:49 chemistry, especially with regard to chemistry and peptides,
10:55:52 and to supervise the research of graduate students and
10:55:57 post-doctorates on those topics.
10:56:06 Q. Prior to moving to MIT, did you teach any classes
10:56:09 relating to peptide chemistry?
10:56:10 A. Yes, I did.
10:56:11 Q. About how many years have you been teaching those
10:56:14 classes?
10:56:15 A. Approximately 30 years.
10:56:16 Q. What is the primary focus of your research, Dr.
10:56:18 Raines?
10:56:18 A. My research is to primarily explain the biological
10:56:23 phenomenon of the principals of chemistry with a focus
10:56:30 peptides and proteins.
10:56:31 Q. How does your research relate to potential therapies?
10:56:35 A. My research is typically translation the sense that we
10:56:39 are also seeking to create the peptides that we create as
10:56:44 potential therapeutic agents.
10:56:45 Q. Can we turn to DTX-316 of your binder. We will put it
10:56:50 up on the screen. Dr. Raines, what is this exhibit?
10:56:53 A. This is my curriculum vitae.
10:56:55 Q. Did you prepare it?
10:56:56 A. Yes, I did.
10:56:57 Q. Does it accurately reflect your education and
10:56:59 experience?

10:57:00 A. **It does.**

10:57:00 Q. **Can you describe your educational background?**

10:57:03 A. **Yes. I have received Bachelor's degrees in chemistry and biology from MIT, as well as Master's and Ph.D. degrees in chemistry from Harvard University.**

10:57:19 Q. **What are your responsibilities as an associate member of the Broad Institute at MIT and Harvard?**

10:57:26 A. **My responsibilities are to interact and confer with Broad scientists, as we together try to come up with and develop new therapies, cutting edge therapies.**

10:57:37 Q. **How long have you been at MIT?**

10:57:39 A. **I returned for MIT just last summer, in July.**

10:57:47 Q. **Before becoming professor at MIT, what position did you hold?**

10:57:51 A. **So before MIT, I was on the faculty at the University of Wisconsin-Madison, starting in 1989.**

10:58:00 Q. **What were your responsibilities at the University of Wisconsin?**

10:58:02 A. **Again, my responsibilities were to teach classes in the chemistry and biology of peptides and proteins, and to supervise research in those areas.**

10:58:14 Q. **Did you have any positions before joining the faculty at the University of Wisconsin?**

10:58:18 A. **I did.**

10:58:20 Q. **What were those positions?**

10:58:22 A. **I was a post-doctorate after I got my Ph.D. for three**
10:58:26 **years at the University of California in San Francisco,**
10:58:29 **working in the Department of Biochemistry and Biophysics.**
10:58:32 Q. **What was the focus of your post-doctorate work?**
10:58:36 A. **Again, my post-doctorate was focused on peptides and**
10:58:41 **proteins, engineering them for potential therapeutic use,**
10:58:47 **and doing research on peptides as well.**
10:58:50 Q. **Was your postdoctoral position the first position**
10:58:53 **after you completed your education?**
10:58:55 A. **Yes.**
10:58:56 Q. **Other than your role as a professor at MIT, do you**
10:58:59 **hold any other positions?**
10:59:00 A. **I do. I am the founder of three start-up companies.**
10:59:08 **Quintessence Biosciences, Hyrax Energy, and Ghost Proteins.**
10:59:14 **I am also now a Professor Emeritus at the University of**
10:59:18 **Wisconsin-Madison.**
10:59:19 Q. **What is the goal of Quintessence Biosciences?**
10:59:22 A. **The goal of Quintessence Biosciences is to develop**
10:59:27 **proteins as potential key therapeutic agents for the**
10:59:29 **treatment of cancer. And we have a protein that's been used**
10:59:33 **to treat 55 patients so far in the clinic.**
10:59:36 Q. **What is the goal of Ghost Proteins?**
10:59:39 A. **The goal of Ghost Proteins is to develop technology,**
10:59:44 **to mask proteins so that they can enter human cells readily,**
10:59:50 **and thereby do what we like to refer to as gene therapy**

10:59:54 **without the genes.**

10:59:55 **Q. How many years have you been doing work relating to**

10:59:59 **peptides?**

11:00:00 **A. Approximately 30 years.**

11:00:01 **Q. Have you received any notable awards as a result of**

11:00:04 **your research?**

11:00:05 **A. I have.**

11:00:08 **In 2016, I received the Ralph Hirschman Award**

11:00:13 **from the American Chemical Society. The American Chemical**

11:00:18 **Society is the world's largest scientist organization and**

11:00:21 **the Hirschman Award is the biggest award they give out for**

11:00:25 **work on peptides.**

11:00:28 **Then last year, in 2017, I received the Vincent**

11:00:32 **du Vigneaud Awards from the American Peptide Society, a**

11:00:35 **group that focuses on peptide research.**

11:00:39 **Q. Have you written any articles during your career?**

11:00:41 **A. Yes, I have.**

11:00:42 **Q. How many?**

11:00:44 **A. I have coauthored approximately 350 articles.**

11:00:49 **Q. Is any of your research subject to patent protection?**

11:00:52 **A. Yes, it is.**

11:00:53 **Q. Did you participate when those patents were being**

11:00:55 **prosecuted at the Patent Office?**

11:00:57 **A. Yes, I did.**

11:00:58 **Q. How did you participate?**

11:01:01 A. **I would disclose an invention to the university,**
11:01:06 **typically, then participate in the drafting of the**
11:01:12 **application, typically with counsel, and finally respond to**
11:01:17 **office actions when that was appropriate.**
11:01:21 Q. **Looking back at your C.V., DTX-316, does it describe**
11:01:25 **the publications and patents we have just been discussing?**
11:01:28 A. **Yes, it does.**
11:01:29 **MR. STULL: I offer Dr. Raines as an expert in**
11:01:31 **the field of peptide chemistry and drug design and**
11:01:36 **discovery.**
11:01:37 **MR. HAUG: No objection, Your Honor.**
11:01:38 **THE COURT: The Doctor is accepted as an expert**
11:01:40 **in those fields.**
11:01:42 **BY MR. STULL:**
11:01:42 Q. **Can you look at JTX-1 in your binder, Dr. Raines. We**
11:01:46 **will put it on the screen.**
11:01:50 A. **Yes.**
11:01:50 Q. **What is JTX-1?**
11:01:52 A. **JTX-1 is the '333 patent.**
11:01:55 Q. **Dr. Raines, have you had slides prepared to assist you**
11:02:00 **in your testimony today?**
11:02:01 A. **I have.**
11:02:01 Q. **Can we look at the first slide, please. Do you have**
11:02:06 **an understanding of which claims of the '333 patent**
11:02:09 **Plaintiffs are asserting in this case?**

11:02:12 A. **Yes, my understanding is they are asserting Claim 14.**

11:02:15 Q. **What is Claim 14 drawn to?**

11:02:19 A. **Claim 14 is drawn to the icatibant peptide.**

11:02:22 Q. **Have you reviewed the prosecution history of the '333 patent?**

11:02:25

11:02:26 A. **Yes.**

11:02:26 Q. **Did you form any opinions about the prosecution history about the '333 patent?**

11:02:28

11:02:31 A. **I did.**

11:02:31 Q. **What are you prepared to testify about today regarding the '333 patent prosecution history?**

11:02:36

11:02:39 A. **I am prepared to testify that from 1991 to 1995, applicants were in possession of scientific data that were responsive to rejections from the Patent Office and did not respond with these data for over four years, and that there is no scientific reason that the responses by applicants in 1995 and later in the prosecution history could not have been made earlier.**

11:02:43

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11:03:02 Q. **In your analysis, did you use a particular definition of a person of ordinary skill in the art?**

11:03:06

11:03:08 A. **I did.**

11:03:09 Q. **What qualifications would render -- would a person of ordinary skill in the art have under your definition?**

11:03:13

11:03:17 A. **A person of ordinary skill in the art would have the qualifications of a Ph.D. in organic chemistry, medicinal**

11:03:19

11:03:23 **chemistry, pharmacology, or a related field; and years of**
11:03:26 **experience in medicinal chemistry or pharmacology relating**
11:03:30 **to peptides; and experience developing new potential drug**
11:03:33 **candidates.**
11:03:34 Q. **Are there any other characteristics that a person of**
11:03:36 **ordinary skill in the art would have?**
11:03:38 A. **Yes. A person of ordinary skill would have regularly**
11:03:41 **reviewed literature related to organic and medicinal**
11:03:44 **chemistry, including peptide chemistry, and would have been**
11:03:46 **able to analyze and characterize potential drug compounds,**
11:03:49 **both structurally and with regard to their biological**
11:03:51 **properties.**
11:03:51 Q. **Do you understand that plaintiffs experts have applied**
11:03:54 **a different definition of a person of ordinary skill?**
11:03:57 A. **Yes, I do.**
11:03:58 Q. **Would your opinions change if you were to apply the**
11:04:02 **plaintiffs' definition of a person of ordinary skill in the**
11:04:04 **art?**
11:04:04 A. **No, they would not.**
11:04:05 Q. **Dr. Raines, do any of the applications in the '333**
11:04:08 **patent prosecution history include testing results?**
11:04:11 A. **Yes, they do.**
11:04:12 Q. **Can you look at JTX-A, Tab A in your binder. What is**
11:04:23 **JTX-A, Dr. Raines?**
11:04:29 A. **JTX-6A.**

11:04:36 Q. **Sorry.**

11:04:39 A. **This is the prosecution history of the '162 patent --**

11:04:53 **sorry. Would you ask that question again?**

11:04:55 Q. **Sure. What is this document?**

11:04:58 A. **This document is the prosecution history of the '052,**

11:05:08 **'149, and '162 applications.**

11:05:10 Q. **Have you reviewed the prosecution history of the '162,**

11:05:13 **'149 and '052 applications?**

11:05:15 A. **Yes, I have.**

11:05:16 Q. **Can you look at JTX-6A, Tab 4 in your binder, that is**

11:05:22 **Pages 5 through 60? We will put it on the screen.**

11:05:24 A. **Yes.**

11:05:24 Q. **What is this document?**

11:05:25 A. **This is prosecution history of the '162 patent**

11:05:28 **application.**

11:05:30 Q. **When was the '162 application filed?**

11:05:35 A. **The '162 application was filed on June 30th, 1989.**

11:05:43 Q. **Let's take a look at Example 59 of the '162**

11:05:47 **application. That is on Page 4 of JTX-6A. What compound is**

11:05:53 **Example 59, Dr. Raines?**

11:05:56 A. **So Example 59 is the icatibant peptide we have seen**

11:06:01 **before.**

11:06:01 Q. **That is Page 40, not 4, excuse me. Is icatibant**

11:06:06 **claimed in the '162 application?**

11:06:08 A. **It is in the genus of claims for the '162 application.**

11:06:12 Q. **Let's take a look at Table 1 from the specification of**
11:06:17 **the '162 application on the screen. That is Pages 27 and 28**
11:06:22 **of JTX-6A. Doctor Raines, what is disclosed in Table 1?**
11:06:27 A. **So Table 1 discloses a list of amino acid sequences,**
11:06:34 **peptides related to bradykinin, potential bradykinin**
11:06:42 **antagonists, along with IC_{50} data reporting their efficacy in**
11:06:47 **an assay.**
11:06:48 Q. **Let's take a look at the third paragraph of Page 26 in**
11:06:53 **JTX-6A. We will put it on the screen here for you. What**
11:07:00 **kind of test was used to generate the data in Table 1 of the**
11:07:03 **specification?**
11:07:05 A. **So the data in Table 1, which we just looked at, was**
11:07:10 **generated by an in vitro assay involving arteries extracted**
11:07:16 **from guinea pigs.**
11:07:17 Q. **Does the '162 application include any results from in**
11:07:22 **vivo testing?**
11:07:22 A. **No, it does not.**
11:07:23 Q. **Did the Patent Office issue any office actions in the**
11:07:29 **'162 application?**
11:07:30 A. **Yes, they did.**
11:07:31 Q. **Can you look at Tab E in your binder of JTX-6A, which**
11:07:37 **is Pages 152 through 159?**
11:07:42 A. **Yes.**
11:07:42 Q. **What is this document, Dr. Raines?**
11:07:47 A. **This is the office action issued by the United States**

11:07:52 **Patent Office with regard to the '162 application.**

11:07:54 Q. **When was this office action mailed?**

11:07:57 A. **This office action was mailed on August 17th, 1990.**

11:08:03 Q. **We are going to look at a passage from this office**

11:08:07 **action on page a 154, JTX-6A. Dr. Raines, what do we see**

11:08:18 **here?**

11:08:19 A. **Well, at the top we see that the patent examiner is**

11:08:23 **rejecting Claims 1 through 6 based on a lack of utility.**

11:08:29 Q. **In the second passage that is highlighted there, what**

11:08:33 **was the scientific basis for this rejection?**

11:08:37 **MR. HAUG: Objection as to form. I don't know**

11:08:39 **how this witness can answer a question about what the**

11:08:42 **scientific basis was for what the examiner did.**

11:08:45 **THE COURT: Fair enough. Ask you to rephrase.**

11:08:49 **BY MR. STULL:**

11:08:49 Q. **Dr. Raines, what was the basis for this rejection?**

11:08:56 A. **The basis for this rejection was a scientific one, as**

11:08:59 **I read it. The examiner is calling for in vivo data, it's**

11:09:05 **underlined twice in this highlighted passage, saying that**

11:09:09 **the in vitro data provided by the applicants using the assay**

11:09:15 **I just described was not enough to demonstrate utility of**

11:09:20 **the invention.**

11:09:20 Q. **As of the date of this office action, August 17th,**

11:09:24 **1990, were applicants in possession of in vivo data for**

11:09:29 **bradykinin antagonist peptides disclosed in this**

11:09:32 application?
11:09:33 A. Yes, they were.
11:09:33 Q. How do you know that?
11:09:35 A. Because I have read some literature, in particular, the article by Wirth and coworkers, that Dr. Bachovchin
11:09:40 talked about yesterday.
11:09:51 Q. Let's take a look at DTX-50 in your binder, please.
11:09:51 We will put it on the screen. What is DTX-50, Dr. Raines?
11:09:57 A. This is the article I was just referring to, the
11:10:04 article by Wirth and coworkers, describing in vivo data
11:10:10 regarding HOE 140, which we heard yesterday is another name
11:10:14 for icatibant.
11:10:20 Q. Who are the authors of this publication?
11:10:21 A. The authors of this publication are scientists from
11:10:25 Hoechst, I have mentioned Dr. Wirth, the last author is Dr.
11:10:30 Scholkens.
11:10:35 Q. Are any of the authors inventors of the '333 patent?
11:10:35 A. Yes, many of these authors are inventors of the '333
11:10:39 patent, and were also listed on the '162 application.
11:10:43 Q. Let's take a look at Statement 1 at the top of the
11:10:46 first page. Dr. Raines, what is being described here?
11:10:50 A. So this is an abstract at the top of the paper. And
11:10:56 the first sentence is telling readers what to look for in
11:11:01 this abstract. In particular, the authors are telling
11:11:05 readers that the icatibant peptide is a highly potent
11:11:09

11:11:16 **bradykinin antagonist, as tested in in vivo assays.**

11:11:21 Q. **Let's take a look at Statement 2, right below that.**

11:11:25 **What's described here?**

11:11:28 A. **Here the authors are going into the next level of**

11:11:32 **detail, describing that icatibant is a potent bradykinin**

11:11:39 **antagonist in assays performed in live rats. It's**

11:11:44 **inhibiting the bradykinin induced hypotensive responses in**

11:11:49 **the rats much more so than about a control peptide.**

11:11:53 Q. **Let's look at Statement 3 below that what is described**

11:11:59 **here?**

11:12:00 A. **So this statement is again saying that the icatibant**

11:12:09 **peptide is an effective agent in tests in live animals.**

11:12:17 **Here the tests are being done in guinea pigs, a different**

11:12:21 **animal, the test is a different assay, it is intended to**

11:12:25 **look at reversing the effect at bradykinin induced**

11:12:31 **bronchoconstriction.**

11:12:32 **Again, the authors believe that icatibant**

11:12:35 **performs extremely well in this in vivo assay.**

11:12:39 Q. **Let's look at Statement 4 below that. What's**

11:12:43 **described here, Dr. Raines?**

11:12:45 A. **It's very comforting that there is yet a third**

11:12:49 **distinct in vivo assay reported in this paper. This one**

11:12:53 **involves rat paws and reversing the edema induced in rat**

11:13:01 **paws.**

11:13:02 **Edema is another word for swelling. Reversing**

11:13:06 **the swelling in the rat paw with the treatment of icatibant,**
11:13:12 **by icatibant.**
11:13:12 Q. **How many in vivo tests of icatibant are described in**
11:13:19 **the work here, in this part of DTX-50?**
11:13:24 A. **There are three distinct in vivo tests of the efficacy**
11:13:33 **of icatibant in vivo assays in the Wirth paper.**
11:13:33 Q. **Let's take a look at the last page, Page 4 of the**
11:13:38 **Wirth article. Looking at the bottom right-hand corner.**
11:13:41 **When was the in vivo data in this article submitted?**
11:13:43 A. **The in vivo data was submitted at least by July 25,**
11:13:51 **1990. That is the date the article was received, the**
11:13:55 **manuscript was received by the journal.**
11:13:56 Q. **As of the August 17th, 1990 office action we have just**
11:14:01 **looked at, were applications in possession of in vivo data**
11:14:05 **for icatibant?**
11:14:06 A. **Yes, they were.**
11:14:07 Q. **How do we know that?**
11:14:09 A. **Because this article had been submitted approximately**
11:14:11 **a month earlier to a very respected journal.**
11:14:15 Q. **Did the August 17th, 1990 office action include any**
11:14:19 **other rejections other than the Section 101 rejection we**
11:14:21 **looked at?**
11:14:22 A. **Yes, it did.**
11:14:25 Q. **Can you look at Tab F of JTX-6A, that is Pages 221**
11:14:41 **through to 40?**

11:14:43 A. **Yes.**

11:14:43 Q. **What is Tab F?**

11:14:46 A. **Tab F is the response to the office action from the**

11:14:49 **applicants regarding their '162 application.**

11:14:54 Q. **Let's look at the last page of the response, Page 240,**

11:15:00 **JTX-6A. When did applicants submit this response?**

11:15:07 A. **They submitted this response on February 19th, 1991.**

11:15:10 Q. **Let's take a look at Page 233 of the response. At the**

11:15:16 **beginning of the first paragraph, Page 233, the first full**

11:15:21 **paragraph, that is, what is being described here, Dr.**

11:15:24 **Raines?**

11:15:25 A. **This is part of the response. And the applicants are**

11:15:30 **stating that they believe that the in vitro data which we**

11:15:36 **have already gone over was in their original application**

11:15:41 **would suffice to overcome the examiner's call for utility.**

11:15:46 Q. **In this response, did applicants provide any in vivo**

11:15:51 **data in response to the office we had looked at?**

11:15:54 A. **No, they did not.**

11:15:54 Q. **Can you look at Page 235, specifically, at the**

11:15:59 **paragraph starting with "The examiner." Did applicants**

11:16:08 **address the scientific reasons for the rejections other than**

11:16:11 **the 101 rejection in this response?**

11:16:15 A. **Yes, they did.**

11:16:16 Q. **Can you turn to tab G of JTX-6A. That is Pages 247**

11:16:24 **through 255?**

11:16:29 A. **I am there.**

11:16:30 Q. **Dr. Raines, what is this document?**

11:16:33 A. **This is an office action written by the U.S. PTO, it's a second office action, a final office action, for the '162 application.**

11:16:44 Q. **When was this office action mailed?**

11:16:48 A. **This office action was mailed on May 31st, 1991.**

11:16:53 Q. **Let's look at a passage from this office action on Pages 248 and 250, we have that up here on the screen. The first statement from Page 248, what do we see here, Dr. Raines?**

11:17:08 A. **Well, we see that the examiner is rejecting claims based on lack of utility.**

11:17:17 Q. **The second statement there?**

11:17:20 A. **So, as before, the examiner is calling for the applicants to provide in vivo data to support the utility, the scientific utility of their invention.**

11:17:34 Q. **Were applicants in possession of scientific information responsive to this request at the time of this office action?**

11:17:40 A. **Yes, they were.**

11:17:41 Q. **And how do you know that?**

11:17:43 A. **Because they had previously submitted the Wirth article, the date of that was July 25th, 1990, before receiving this office action.**

11:17:53

11:17:54 Q. **Did applicants provide scientific information responsive to this request?**

11:17:58 A. **No, they did not.**

11:18:00 Q. **Were there rejections other than the 101 rejection in those 1991 office actions?**

11:18:06 A. **Yes, they were.**

11:18:08 Q. **Did applicants address the scientific reasons for those rejections?**

11:18:11 A. **No, they did not.**

11:18:12 Q. **Following this office action, did a patent issue from the '162 application?**

11:18:16 A. **No. This application was abandoned.**

11:18:18 Q. **Did you prepare a slide describing the applications in the '333 patent prosecution history?**

11:18:21 A. **I did.**

11:18:24 Q. **Next slide. Is that also shown on the board over here?**

11:18:27 A. **Yes, it is.**

11:18:28 Q. **Taking a look at this prosecution history flowchart of the '333 patent, where does the '162 application we just looked at fit into the flowchart?**

11:18:32 A. **The '162 application is the very first one in the upper left here on my poster. It's labeled No. 1. It's the one that was submitted on June 30th, 1989.**

11:18:33 Q. **How many applications were filed during the '333**

11:18:40

11:18:45

11:18:47

11:18:50

11:18:54

11:18:57

11:19:00 patent prosecution history?
11:19:02 A. As you can see here, because I have numbered them,
11:19:04 there were 11 applications that were filed.
11:19:07 Q. How many patents issued from the 11 applications in
11:19:11 the '333 patent prosecution history?
11:19:14 A. Only one patent issued, the '333 patent.
11:19:17 Q. And the slide we are looking at here is DDX4-5. Can
11:19:25 you explain how you organized the applications in the '333
11:19:29 patent prosecution history?
11:19:31 A. To try to simplify this, I have organized the
11:19:34 applications into three groups. And those groups are based
11:19:41 on the amino acid sequences of the peptides that are within
11:19:46 the examples of the application.
11:19:48 Q. Did you prepare a slide describing the different
11:19:50 groups?
11:19:51 A. I did.
11:19:52 Q. The next slide, please.
11:19:54 What defines Group I, Dr. Raines?
11:19:58 A. So Group I, as is shown on this slide, always has a
11:20:03 D-Tic residue at position No. 7. And the other amino acids
11:20:09 in this ten-residue peptide could vary, lot of variation in
11:20:17 those other residues.
11:20:18 Q. For the record, this is Slide DDX4-6.
11:20:24 What defines Group II, Dr. Raines?
11:20:27 A. The Group II peptides all have a D-Phe, a

11:20:31 **D-phenylalanine at position 7, and again, there are lots of**
11:20:37 **possibilities for the other amino acids. I am just showing**
11:20:41 **one example here to make it more simple.**
11:20:43 Q. **What defines Group III?**
11:20:46 A. **Group III is a little different. Again, there is a**
11:20:49 **D-Tic residue at position 7. There are a limited number of**
11:20:56 **residues at Position 5, a leucine and a handful of other**
11:21:01 **amino acids, and much less variability than the Group I and**
11:21:05 **Group II. But those make Group III distinct.**
11:21:09 Q. **Did any of the groups include the peptide icatibant?**
11:21:13 A. **Yes.**
11:21:13 Q. **What group?**
11:21:15 A. **Group I.**
11:21:17 Q. **Looking back at the flow cart on the board here, what**
11:21:21 **applications have you organized in Group II?**
11:21:24 A. **In Group II I have organized the '270 application, and**
11:21:29 **the '090 application.**
11:21:32 Q. **When was the '270 application filed?**
11:21:35 A. **The '270 application was filed on August 10th, 1990.**
11:21:39 Q. **When was the '090 application filed?**
11:21:42 A. **February 18th, 1992.**
11:21:45 Q. **What applications have you organized in Group III?**
11:21:49 A. **In Group III are the '297 application, the '766**
11:21:54 **application, and the '523 application.**
11:21:58 Q. **When was the '297 application filed?**

11:22:01 A. **On April 24th, 1991.**

11:22:05 Q. **When was the '766 application filed?**

11:22:08 A. **On March 2nd, 1992.**

11:22:10 Q. **And when was the '523 application filed?**

11:22:15 A. **On October 30, 1992.**

11:22:17 Q. **Did the Patent Office issue office actions in the Group II and Group III applications we just talked about?**

11:22:23 A. **Yes, they did.**

11:22:24 Q. **Did applicants address the scientific reasons for the rejections and office actions in the Group II and Group III applications?**

11:22:32 A. **No, they did not.**

11:22:36 Q. **Can I get the next slide, please, Mr. Chase.**

11:22:41 **This is Slide DDX4-7. How many applications in the prosecution history of the '333 patent did applicants address the scientific reasons for rejections from office actions?**

11:22:53 A. **The applications --**

11:22:55 **MR. HAUG: Objection to the extent it requires this witness to opine on what all the rejections may have been in all of these 11 applications.**

THE COURT: Read the question.

11:23:49 **(Pending question read.)**

11:23:49 **THE COURT: What is your objection, Mr. Haug?**

11:23:51 **MR. HAUG: My objection is the question assumes**

there were objections and asking for scientific reasons. It's lack of foundation.

THE COURT: I think that's the objection.

MR. STULL: We can get to it later.

MR. HAUG: I withdraw the objection. It is really lack of foundation.

THE COURT: He said he will get to it later. Either way you wish to do it is fine, counsel.

BY MR. STULL:

Q. Following the '162 application we just looked at, what was the next application in Group I?

A. The next application was the '149 application.

Q. When was the '149 application filed?

A. The '149 application was filed on August 14th, 1991.

Q. Can you turn back to JTX-6A, Tab H, which is Pages 323 through 331?

A. Yes.

Q. What is this document, Dr. Raines?

A. This is a preliminary amendment that was the basis for the '149 application.

Q. Can you look at Page 331 of this preliminary amendment?

A. Yes.

Q. When was the preliminary amendment filed?

A. August 14, 1991.

11:25:09 Q. **Looking back at the first page of the preliminary**
11:25:12 **amendment, which is Page 323, right below the line where it**
11:25:17 **says in the specification, what's being described here, Dr.**
11:25:23 **Raines?**
11:25:23 A. **So what's being described here are additional examples**
11:25:32 **that are now a part of the '149 application, including, we**
11:25:39 **see here Example 165, peptide sequence, amino acid sequence**
11:25:45 **that is a putative bradykinin antagonist.**
11:25:50 Q. **Let's look at the table on Pages 328 and 329. We will**
11:25:55 **put them on the screen here. What is being described in**
11:25:58 **this table?**
11:26:00 A. **So in this table is described some scientific data**
11:26:05 **that reports in vitro testing results for the additional**
11:26:14 **peptides being added to the application as well as**
11:26:19 **reiterating some data from the previous application.**
11:26:22 Q. **Did this preliminary amendment to the '149 application**
11:26:26 **add any in vivo data?**
11:26:27 A. **No, it did not.**
11:26:28 Q. **Did the Patent Office issue any office actions in the**
11:26:32 **'149 application?**
11:26:33 A. **No, they did not. Sorry, yes, they did. I misspoke.**
11:26:39 Q. **Let's look at Tab I of JTX-6A. It's Pages 468 through**
11:26:46 **479. What is this document?**
11:26:54 A. **This document is the office action that I was just**
11:26:59 **speaking about. This is the office action issued by the**

11:27:03 **U.S. PTO in response to the '149 application.**

11:27:05 Q. **When was this office action mailed?**

11:27:08 A. **On July 1st, 1992.**

11:27:11 Q. **Can you look at these passages we are going to put on the screen from Pages 470 through 471 of JTX-6A. The first one starts with Claims 5 and 6 there. What do we see here, Dr. Raines?**

11:27:25 A. **We see that the patent examiner is rejecting claims based on lack of utility.**

11:27:32 Q. **And in the second statement, that starts one skilled in the art, what is the scientific basis provided in this rejection?**

11:27:39 A. **The underlying science here is that the examiner again is asserting that the in vitro data is not enough, the examiner is calling for the applicants to provide in vivo data as a demonstration of utility.**

11:27:58 Q. **Is this similar to the rejection made in the earlier '162 application?**

11:28:03 A. **Yes, it is.**

11:28:05 Q. **Were applicants in possession of data responsive to the request in this office action?**

11:28:09 A. **Yes, they were.**

11:28:10 Q. **Did applicants provide scientific information in response to this request from the Patent Office?**

11:28:21 A. **No.**

11:28:21 Q. **Let's look at Page 471 from JTX-6A, the bottom of the**
11:28:28 **page. Were there any other rejections in this office**
11:28:30 **action?**
11:28:30 A. **Yes, there were.**
11:28:31 Q. **Did applicants address the scientific reasons for the**
11:28:35 **other rejections?**
11:28:36 A. **No, they did not.**
11:28:37 Q. **Did a patent issue from the '149 application following**
11:28:40 **this office action?**
11:28:41 A. **No, this application was abandoned.**
11:28:44 Q. **Let's look back at the board after the '149**
11:28:54 **application we just looked at, which was No. 4 on your**
11:28:58 **group, what was the next Chart I application?**
11:29:00 A. **The next application that I put into Group I was the**
11:29:03 **'052 application.**
11:29:05 Q. **When was the '052 application filed?**
11:29:09 A. **On November 25, 1992.**
11:29:12 Q. **Did the Patent Office issue any office actions in the**
11:29:16 **'052 application?**
11:29:18 A. **Yes, they did.**
11:29:19 Q. **Can you look at Tab J in JTX-6A?**
11:29:25 A. **I am there. That is Pages 497 through 598 of JTX-6A.**
11:29:33 Q. **What is this document, Dr. Raines?**
11:29:35 A. **This is a copy of the office action from the United**
11:29:39 **States Patent Office regarding the '052 application.**

11:29:41 Q. **When was the office action mailed?**

11:29:43 A. **On February 8, 1993.**

11:29:45 Q. **Can we look at the passage from Page 499 of JTX-6A, the passage starts with Claims 5 and 6. We have it there on the screen. What do we see here, Dr. Raines?**

11:29:58 A. **We see, again, the examiner is stating that claims in the application are rejected because of a lack of utility.**

11:30:08 Q. **If we look at the second statement from Pages 499 to 500, what was the basis for this rejection?**

11:30:16 A. **The basis, once again, is that the application contains in vitro data but not the in vivo data. And I found it interesting that the words here are word for word identical in this '052 office action as in the '149 office action.**

11:30:36 Q. **Was this rejection also similar to the earlier '162 application?**

11:30:40 A. **Yes, it was.**

11:30:43 Q. **Were applicants in possession of scientific information responsive to this request from the Patent Office?**

11:30:49 A. **Yes, they were.**

11:30:50 Q. **Doctor, did applicants provide scientific information responsive to this request from the Patent Office?**

11:30:56 A. **No, they did not.**

11:30:58 Q. **Looking at the bottom of Page 500 of JTX-6A and**

11:31:08 looking at the paragraph following, were there any other
11:31:13 rejections included in this office action?
11:31:15 A. Yes, there were.
11:31:15 Q. Did applicants address the reasons for any of the
11:31:18 other rejections in this office action?
11:31:19 A. No, they did not.
11:31:21 Q. We are going to go back to the flowchart now again.
11:31:26 Did a patent issue from the '052 application
11:31:30 following the office action we just looked at?
11:31:36 A. No, no patent issued and this application was
11:31:41 abandoned.
11:31:41 Q. Was there another Group I application after the '052
11:31:45 application?
11:31:46 A. No, there wasn't.
11:31:46 Q. Can you explain that?
11:31:48 A. At this stage, the applicants combined the examples
11:31:55 from their three different groups into a single application,
11:31:59 and I have indicated that here in the bottom of my slide and
11:32:05 my chart as the combined Groups I, II and III.
11:32:09 Q. In what application did applicants first combine those
11:32:13 groups?
11:32:13 A. That would be the '849 application.
11:32:19 Q. When was the '849 application filed?
11:32:22 A. On February 3, 1993.
11:32:23 Q. Can you look at JTX-7A, Tab A, and specifically at

11:32:33 **Pages 1 through 3 in your binder.**

11:32:40 **What is JTX-7A, Dr. Raines?**

11:32:43 A. **This document is the prosecution history for the '849 and '018 applications.**

11:32:47

11:32:49 Q. **Did you review the prosecution histories of the '849 and '018 applications?**

11:32:53

11:32:55 A. **I did.**

11:32:56 Q. **Did the Patent Office issue any office actions in the '849 application?**

11:32:59

11:33:01 A. **Yes, they did.**

11:33:01 Q. **Can you look at Tab D of JTX-7A? That is Page 217 through 232.**

11:33:09

11:33:13 A. **I am there.**

11:33:13 Q. **What is this document?**

11:33:14 A. **This is a copy of the office action from the U.S PTO regarding the '849 application.**

11:33:19

11:33:22 Q. **When was this office action mailed?**

11:33:24 A. **On November 3rd, 1993.**

11:33:27 Q. **Let's look at a passage from this office action from Page 219, the first passage will be Claims 1 through 34....**

11:33:31

11:33:38 **What do we see there, Dr. Raines?**

11:33:42 A. **Well, we see here again claims are being rejected by the patent examiner for a lack of utility.**

11:33:46

11:33:50 Q. **To look at the second statement, starting with "One skilled in the art," what was the scientific basis provided**

11:33:55

11:33:58 **for this rejection?**

11:33:59 A. **The basis, once again, was the absence of in vivo data**

11:34:06 **in the application.**

11:34:07 Q. **Is this similar to the 101 rejections made in the**

11:34:11 **earlier '162, '149 and '052 applications we looked at?**

11:34:18 A. **In my scientific judgment, it is.**

11:34:19 Q. **Were applicants in possession of scientific**

11:34:21 **information responsive to this request?**

11:34:25 A. **Yes, they were.**

11:34:26 Q. **Did applicants provide scientific information**

11:34:29 **responsive to this request in the '849 application?**

11:34:32 A. **No, they did not.**

11:34:33 Q. **Can you look at Page 221 of JTX-7A, about halfway**

11:34:41 **down, starting with the sentence, "The following."**

11:34:44 **Were there any other rejections included in this**

11:34:47 **office action?**

11:34:48 A. **Yes, there were.**

11:34:48 Q. **Did applicants address any of the scientific reasons**

11:34:51 **for the other rejections?**

11:34:52 A. **No, they did not.**

11:34:53 Q. **Looking back at the chart again, the flowchart, did a**

11:35:00 **patent issue from the '849 application, the one you have**

11:35:03 **labeled 9?**

11:35:04 A. **No, it did not. That was abandoned.**

11:35:06 Q. **After the '849 application, what was the next**

11:35:12 application in the '333 patent prosecution history?
11:35:15 A. The next application was the '018 application,
11:35:19 application No. 10 on my chart.
11:35:23 Q. When was the '018 application filed?
11:35:26 A. May 2nd, 1994.
11:35:28 Q. Did the Patent Office issue any office actions in the
11:35:32 '018 application?
11:35:33 A. Yes, they did.
11:35:35 Q. Let's turn to Tab E in JTX-7A, which is Pages 246
11:35:43 through 260. What is the document, Dr. Raines?
11:35:46 A. This is a copy of the office action issued by the
11:35:49 USPTO in regard to the '018 application?
11:35:54 Q. When was this office action mailed?
11:35:55 A. This office action was mailed on December 6, 1994.
11:35:59 Q. Let's look at a passage from this office action, at
11:36:04 Page 248, starting with the first passage, where it says
11:36:08 Claims 1 through 34. What do we see here, Dr. Raines?
11:36:13 A. We see that, again, claims are being rejected by the
11:36:17 examiner for lack of utility.
11:36:19 Q. What was the scientific basis for this rejection?
11:36:24 A. Again, the examiner is noting that the applicants have
11:36:30 not provided in vivo data to support the utility of the
11:36:37 invention. Again, it struck me that the wording here is
11:36:40 word for word identical as in response to the '018
11:36:46 application as the '849 application.

11:36:50 Q. **Is this similar to the rejections for the other three**
11:36:55 **applications, the '052, '149, and '162 applications?**
11:36:55 A. **Yes.**
11:36:55 Q. **Were applicants in possession of scientific**
11:36:58 **information responsive to this request in this office**
11:37:00 **action?**
11:37:01 A. **Yes, they were.**
11:37:01 Q. **And how do you know that?**
11:37:05 A. **Because they had now long ago submitted and published**
11:37:10 **the article that I have been calling the Wirth article.**
11:37:13 Q. **And that's DTX-50 in your binder?**
11:37:17 A. **Yes.**
11:37:17 Q. **Can you look at Page 250, JTX-7A, where it starts "The**
11:37:26 **following," were there any other rejections included in this**
11:37:30 **office action?**
11:37:31 A. **Yes, there were.**
11:37:31 Q. **Can you turn to Tab G at JTX-7A, that is Page 263**
11:37:40 **through 314. Dr. Raines, what is this document?**
11:37:51 A. **This is a response to the office action by the**
11:37:57 **applicants.**
11:37:59 Q. **Let's look at Page 314 of this response. When was**
11:38:04 **this response submitted?**
11:38:07 A. **` Was submitted on June 6th, 1995.**
11:38:10 Q. **Did this response address the scientific reasons for**
11:38:14 **rejections from the December 6th, 1994 office action we just**

11:38:18 looked at?
11:38:20 A. Yes, it did.
11:38:21 Q. Did this response provide scientific information that
11:38:24 was responsive to the request in the December 6, 1994 office
11:38:28 action?
11:38:28 A. Yes, it did.
11:38:33 Q. Look at the next slide please, Mr. Chase.
11:38:38 That is DDX-4-9. How long a period of time did
11:38:42 applicants fail to provide scientific data responsive to
11:38:47 rejections in office actions during the '333 patent
11:38:50 prosecution history?
11:38:51 A. A bit over four years.
11:38:31 Q. And how long a period of time did applicants fail to
11:38:39 address the scientific reasons for any of the rejections in
11:38:42 office actions in the '333 patent prosecution history?
11:38:46 A. Over four years.
11:38:47 Q. And how did you determine that period of time?
11:38:49 A. So I calculated that based on the date of the office
11:38:55 action to the '162 application, that was the first
11:39:01 application, and that office action was dated May 31st, 1991
11:39:07 and the four years lapsed until the response that we just
11:39:10 looked at until the '018 application, June 6, 1995.
11:39:17 Q. Turning back to the office action, which is JTX-7A,
11:39:22 Tab G, we're going to look at a passage from Page 299, where
11:39:27 it starts, however, to address.

11:39:30 **What do we see here, Dr. Raines?**

11:39:32 A. **We see here in the response to the office action**

11:39:38 **regarding the '018 application that the applicants are**

11:39:45 **saying that they're addressing the examiner's concerns about**

11:39:51 **the lack of predicted value of in vitro assay by providing a**

11:39:57 **declaration from one of the inventors, Dr. Scholkens.**

11:40:05 Q. **Can you turn to tab H of JTX-7A, pages 327 through**

11:40:12 **331.**

11:40:13 A. **I'm there.**

11:40:13 Q. **What is this document?**

11:40:17 A. **This is the declaration I just referred to regarding**

11:40:24 **the provision of in vivo data.**

11:40:27 Q. **Who is Dr. Scholkens?**

11:40:30 A. **So Dr. Scholkens was an employee at Hoechst. He was**

11:40:36 **an inventor on the patents starting with the '162, the**

11:40:44 **patent application starting with the '162 application, and**

11:40:48 **he was an author of the paper that I've been calling the**

11:40:55 **Wirth 1991 paper.**

11:40:56 Q. **And can we turn to a passage in this declaration at**

11:40:59 **Page 329, and looking at the part, the Paragraph 5 starting**

11:41:04 **with, I studied. Can you explain this statement, Dr.**

11:41:10 **Raines?**

11:41:10 A. **Yes. In his declaration, Dr. Scholkens is stating**

11:41:19 **that he studied the effect of icatibant, again, Hoe 140, on**

11:41:25 **bronchoconstriction as a bradykinin antagonist and that this**

11:41:31 is data that he acquired in vivo, data that he published in
11:41:37 the British Journal of Pharmacology in 1991. This is the
11:41:41 Wirth article that we looked at previously. So he's
11:41:45 bringing this to the attention of the examiner here in his
11:41:53 declaration.
11:41:54 Q. And looking at a passage a little further down on Page
11:42:00 329 going over to Page 330, what does Dr. Scholkens say
11:42:15 about the Wirth 1991 paper?
11:42:17 A. He says that the Wirth 1991 paper clearly shows that
11:42:23 the bradykinin antagonist, Hoe 140, icatibant, worked in
11:42:32 vivo.
11:42:33 Q. Is there any scientific reason or explanation why this
11:42:37 publication, DTX-50, the Wirth article, could not have been
11:42:41 used to respond to office actions as early as 1990?
11:42:45 A. Not that I've seen.
11:42:46 Q. In looking a little further in Paragraph 5 on page 30,
11:42:52 330, excuse me, does Dr. Scholkens cite to any other papers?
11:42:57 A. Yes. He cites in his declaration to a second paper by
11:43:04 Wirth and Hoechst colleagues. This was published in a
11:43:11 different journal, the American Review of Respiratory
11:43:16 Disease, and this article also describes that Hoe 140 has
11:43:25 efficacy in an in vivo model, the kind of information that
11:43:31 the examiner, as we've seen, has been calling for over and
11:43:34 over again.
11:43:36 Q. And when was this second paper published?

11:43:38 A. **This paper was published in 1993.**

11:43:41 Q. **What does Dr. Scholkens say about the second paper, the Wirth 1993 paper?**

11:43:45 A. **Well, again, as you can read on the slide, he says that it presents an in vivo model, and that this is predicted to be, to demonstrate efficacy and to demonstrate therefore utility.**

11:43:48 Q. **And as a scientist, how would you review the relationship between the Wirth 1991 article and the Wirth 1993 article?**

11:43:52 A. **Well, I looked at these articles several times and the 1991 article is a terrific piece of work and more comprehensive than the '93 article. The '93 article is along the same lines. It's a bit confirmatory, I would say, to the 1991 article.**

11:43:55 Q. **Can you turn to JTX-7A, Tab I in your binder?**

11:44:01 A. **Yes.**

11:44:03 Q. **That's pages 342 through 346.**

11:44:10 A. **I'm there.**

11:44:14 Q. **Is this a copy of the Wirth 1993 paper referred to by Dr. Scholkens we were just talking about?**

11:44:15 A. **That is the 1993 paper.**

11:44:19 Q. **And is Dr. Scholkens an author of this paper?**

11:44:27 A. **Yes. He is the last author just as he was in the 1991 paper.**

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11:45:05 Q. **Can you look at the bottom left-hand corner of the**
11:45:07 **first page of the Wirth 1993 article?**
11:45:12 A. **Yes.**
11:45:12 Q. **When was this paper submitted?**
11:45:14 A. **This paper was submitted to the journal on or before**
11:45:20 **December 16th, 1991.**
11:45:23 Q. **Is there any scientific reason or explanation why the**
11:45:26 **data in this publication could not have been cited in**
11:45:29 **response to an office action dating back to December 1991?**
11:45:33 A. **Not that I can see.**
11:45:37 Q. **Is the Wirth 1991 paper cited in the Scholkens**
11:45:42 **declaration responsive to the request for in vivo data from**
11:45:46 **the December 6th, 1994, office action?**
11:45:49 A. **Yes, it is.**
11:45:50 Q. **Is the Wirth 1993 paper cited in the Scholkens**
11:45:53 **declaration responsive to the request for in vivo data from**
11:45:56 **the December 6th, 1994, office action?**
11:45:58 A. **It is.**
11:45:59 Q. **Why is it responsive?**
11:46:01 A. **So these two papers report exactly the kind of data**
11:46:06 **the examiner was seeking throughout this prosecution. The**
11:46:14 **papers report in vivo data showing the efficacy of the**
11:46:20 **icatibant peptides.**
11:46:23 Q. **And did the June 6th, 1995, response to office action**
11:46:27 **that included the declaration of Dr. Scholkens we were just**

11:46:30 looking at, did it address the scientific reasons for the
11:46:36 other rejections from December 6th, 1994 office action?
11:46:39 A. Yes.
11:46:39 Q. Is there any scientific reason or explanation why the
11:46:44 arguments in this June 6th, 1995, response could not have
11:46:47 been provided in May 1991?
11:46:49 A. No.
11:46:49 Q. Can you turn to Tab K of JTX-7A, pages 427 through
11:47:03 437. What is this document, Dr. Raines?
11:47:06 A. This is a copy of the second and final office action
11:47:14 from the United States Patent Office regarding the '018
11:47:17 application.
11:47:18 Q. And when was this office action mailed?
11:47:20 A. On November 9th, 1995.
11:47:23 Q. And can you look at a passage from Page 429 of JTX-7A?
11:47:32 That's a paragraph starting with, the 101. What's described
11:47:36 here, Dr. Raines?
11:47:38 A. So the examiner here is stating quite cursorily that
11:47:45 she is withdrawing the 101 rejection based on the
11:47:48 applicants' arguments.
11:47:50 Q. And applicants' arguments included the Scholkens
11:47:54 declaration that we just looked at; is that correct?
11:47:56 A. Yes. That was part of the response.
11:47:59 Q. Which included the citation of Wirth 1991 and Wirth
11:48:02 1993 articles; is that correct?

11:48:03 A. **Yes, that's correct.**

11:48:04 Q. **Going back to the prosecution history flow chart on your board, following the '018 application we just looked at, what was the next application we filed in the '333 patent prosecution history?**

11:48:17 A. **The next application was the '442 application at the bottom of this chart.**

11:48:23 Q. **When was the '442 application filed?**

11:48:27 A. **The '442 application was filed on June 7th, 1995.**

11:48:33 Q. **Can you turn to JTX-2 in your binder, please?**

11:49:00 A. **Yes. I'm there.**

11:49:01 Q. **What is JTX-2, Dr. Raines?**

11:49:05 A. **So JTX-2, you pointed me towards 2A?**

11:49:21 Q. **Just the whole document?**

11:49:23 A. **Oh, the whole document is the -- the prosecution history for the '442 application.**

11:49:30 Q. **Have you every reviewed the prosecution history for the '442 application?**

11:49:34 A. **Yes, I have.**

11:49:35 Q. **Can you turn to Tab F of JTX-2? That's Page 224. We'll put it up on the screen here?**

11:49:45 A. **Yes. I'm there.**

11:49:46 Q. **What is this document, Dr. Raines?**

11:49:52 A. **This document is the notice of allowance issued by the USPTO for the '442 application.**

11:49:57

11:50:02 Q. **And when did the Patent Office mail this notice of allowance?**

11:50:05 A. **This was mailed on December 24th, 1996.**

11:50:06 Q. **And looking back at the flow chart on your board here, and we'll put it on the screen, too, did the '442 application issue as a patent?**

11:50:10 A. **Yes, it did.**

11:50:14 Q. **And what patent is that?**

11:50:18 A. **That is the '333 patent.**

11:50:20 Q. **Can I get the next slide, please, Mr. Chase.**

11:50:22 **After applicants provided in vivo data on June 6, 1995, how long did it take for applicants to get the '333 patent allowed?**

11:50:23 A. **It took about 18 months for the allowance.**

11:50:32 Q. **And just to recap all of the applications that we've gone through, we'll look at the overall prosecution history. Get the next slide.**

11:50:35 **Which applications in the prosecution history did applicants address the scientific reasons for rejections from the Patent Office?**

11:50:40 A. **The applicants addressed the scientific reasons for the rejections from the Patent Office in the first application, that's the '162 application, and the last two of the 11 applications, that's the '018 and the '442 applications.**

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11:51:25 Q. **In your review of the '333 patent prosecution history, have you seen any reason or explanation for applicant's failure to address the scientific reasons for rejections in the office actions from the other eight applications?**

11:51:40 A. **I have not.**

11:51:42 Q. **Is there any scientific reason the arguments presented by applicants during the '018 and '442 application, the last two applications, could not have been advanced in 1991?**

11:51:54 **MR. HAUG: Objection as to form. Scientific reason why something couldn't have been done earlier is not calling for expert testimony.**

11:52:02 **If he's asking his opinion, that's not a scientific opinion. Is --**

11:52:07 **THE COURT: I agree. I agree. Rephrase.**

11:52:13 **BY MR. STULL:**

11:52:23 Q. **Is there any scientific reason or explanation why the arguments presented by applicants during the '018 and '442 applications could not have been advanced in 1991?**

11:52:34 A. **The applicants had no reason. They could have advanced those arguments earlier, so my answer is no.**

11:52:43 Q. **Switching to a little bit different topic. Earlier today and a little bit of yesterday did you hear Dr. Burch testify about work done by Nova pharmaceuticals in the late 1980s and early 1990s?**

11:52:59 A. **Yes, I did.**

11:52:59 Q. **What was Nova Pharmaceutical doing during that period of time?**

11:53:06 A. **Nova Pharmaceutical was developing bradykinin antagonists.**

11:53:09 Q. **Did they publish any papers about the bradykinin antagonists they synthesized?**

11:53:10 A. **Yes, they did.**

11:53:14 Q. **Can we look at JTX-41? And it is a much smaller exhibit.**

11:53:15 A. **I'm there.**

11:53:23 Q. **And what is this document, Dr. Raines?**

11:53:32 A. **This is a copy of a paper published in the British Journal of Pharmacology from scientists at Nova Pharmaceutical Company, reporting data, scientific data on a bradykinin antagonist.**

11:53:32 Q. **When was this published?**

11:53:36 A. **This paper was published in 1991.**

11:53:40 Q. **Who were the authors?**

11:53:44 A. **They were, they included Dr. Burch and other scientists from Nova Pharmaceutical Corporation. I think we saw this paper earlier.**

11:53:50 Q. **And taking a look at the abstract there on the first page, what does this paper describe?**

11:53:53 A. **This paper describes work on a particular bradykinin antagonist at Nova. This is the antagonist known as NPC**

11:54:30 16731, and reports, this abstract reports, as does the
11:54:36 paper, on the efficacy of that antagonist in assays.
11:54:44 Q. Have you prepared a slide showing the amino acid
11:54:47 sequence of NPC 16731?
11:54:50 A. Yes, I have.
11:54:53 Q. What is the amino acid sequence of NPC 16731?
11:54:58 A. D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Tic-Arg.
11:55:07 Q. Go back to the article, JTX 41. In looking at the
11:55:12 second column of Page 1 that starts with bradykinin binding,
11:55:21 what kind of work is being described here, Dr. Raines?
11:55:26 A. So this article describes some procedures for in vitro
11:55:32 assays for efficacy of the peptide I just described NPC
11:55:41 16731 as bradykinin antagonist.
11:55:45 Q. And let's take a look at Page 2 of JTX-41,
11:55:50 specifically at the section where it starts with discussion,
11:55:54 and at the very bottom of the discussion section. Excuse
11:55:59 me. The first paragraph there, Mr. Chase, up there at the
11:56:04 top. Thank you.
11:56:08 A. Yes. The authors are writing here that NPC 16731, the
11:56:15 peptide we've been talking about from Nova, is a bradykinin
11:56:21 receptor antagonist, and not only that, it's significantly
11:56:24 more potent than the control peptide that they used in this
11:56:30 particular setting. In other words, this was a very potent
11:56:35 molecule.
11:56:36 Q. Is NPC 16731 that's described in this paper included

11:56:41 **in a claim of the '333 patent?**

11:56:43 A. **Yes, it is.**

11:56:45 Q. **Can I get the next slide, please.**

11:56:48 **Is NPC 16731 claimed in claim 12 of the '333 patent?**

11:56:56 A. **Yes. It's the fifth peptide sequence listed in claim 12.**

11:57:01 Q. **And I hate to do this, but can you turn back to JTX-6A, Tab B.**

11:57:07 A. **Somehow it's easier going backwards than forwards.**

11:57:12 Q. **Okay.**

11:57:15 A. **I don't know why that is.**

11:57:16 Q. **In looking at the '162 application, which is Tab B, can you turn to page 38. And looking specifically at example 48, Dr. Raines, what compound is Example 48?**

11:57:18 A. **NPC 16731, the peptide we were just talking about from Nova Pharmaceuticals.**

11:57:39 Q. **Was NPC 16731 claimed in applications in the '333 patent prosecution history from the '162 application until the issuance of the '333 patent?**

11:57:45 A. **Yes.**

11:57:50 Q. **Was icatibant claimed in applications in the '333 patent prosecution from the '162 application until the issuance of the '333 patent?**

11:57:54 A. **Yes.**

11:57:56

11:57:57

11:58:01

11:58:05

11:58:06

11:58:11 **MR. STULL: No more questions.**

11:58:12 **THE COURT: Mr. Haug, you can start your**

11:58:13 **cross-examination. We'll go until 12:30.**

11:58:16 **MR. HAUG: Thank you, Your Honor.**

11:58:26 **THE COURT: Do you have an equally big binder?**

11:58:28 **MR. HAUG: Unfortunately, more than equal.**

11:58:30 **THE COURT: Okay. Doctor, you can use the**

11:58:35 **slides over here.**

11:58:36 **THE WITNESS: Thank you.**

11:59:13 **(Binders handed to the Court and to the**

11:59:18 **witness.)**

12:00:11 **THE COURT: How many are we supposed to have,**

12:00:14 **Mr. Haug?**

12:00:15 **MR. HAUG: Three, Your Honor. Three. I kept**

12:00:16 **one back because I don't think I may refer to it.**

12:00:18 **THE COURT: Okay. Appreciate it.**

12:00:20 **MR. HAUG: You have enough, unfortunately.**

12:00:23 **CROSS-EXAMINATION**

12:00:24 **BY MR. HAUG:**

12:00:25 Q. **Okay. Still good morning, Dr. Raines. Okay. I'm Ed**

12:00:31 **Haug representing Shire and Sanofi in the case. I will**

12:00:34 **conduct the cross-examination.**

12:00:35 **At the outset, I'd like to make sure, or try to**

12:00:41 **make sure that I understand your opinion or opinions. All**

12:00:47 **right.**

12:00:47 **Now, am I correct to understand that it is your**
12:00:53 **view that Hoechst, the applicants, were in possession of**
12:00:59 **the Wirth article and the data contained in that article in**
12:01:04 **1991 or '90?**
12:01:06 A. **They submitted a manuscript, the Wirth manuscript, on**
12:01:16 **July 25th, 1990, and so they had the data at least by that**
12:01:21 **date, presumably before that date.**
12:01:24 Q. **And that was DTX-50, I believe, as you just testified**
12:01:27 **about; is that right?**
12:01:28 A. **I will take your word for it.**
12:01:30 Q. **Okay. Thank you.**
12:01:31 **And it's your view that the Wirth article sets**
12:01:40 **forth compelling data showing the efficacy --**
12:01:46 **THE COURT: I don't think he said compelling,**
12:01:47 **but he's perfectly capable of saying what he said. I don't**
12:01:52 **need all of that.**
12:01:53 **MR. HAUG: Thank you, Your Honor. Sorry.**
12:01:55 **BY MR. HAUG:**
12:01:55 Q. **Do you believe the data in the Wirth data is**
12:01:58 **compelling?**
12:01:59 A. **I like the Wirth article. It sets forth data that**
12:02:05 **were clearly responsive to the call for in vivo data by the**
12:02:12 **examiner. The Wirth article reports data, as I mentioned,**
12:02:18 **on three different, for three different types of in vivo**
12:02:22 **assays.**

12:02:23 Q. **All right. The Wirth article is limited to looking at**
12:02:28 **icatibant; isn't that correct?**
12:02:29 A. **Sort of. I believe there was a control peptide in the**
12:02:39 **article as well. Perhaps a peptide from Stewart.**
12:02:44 Q. **And so the Wirth article was comparing activity**
12:02:50 **for icatibant against the Stewart prior compound; is that**
12:02:57 **right?**
12:02:57 A. **Yes. I believe that's true.**
12:03:00 Q. **And it is your opinion that the data contained in the**
12:03:06 **Wirth article was sufficient to respond to what you**
12:03:15 **understand to be the examiner's rejection earlier in the**
12:03:19 **prosecution, as you have testified; is that right?**
12:03:22 A. **I testified that the data in the Wirth article was**
12:03:32 **responsive to the call by the examiner for in vivo data.**
12:03:38 Q. **And that was, that call for in vivo data was part of a**
12:03:43 **rejection under 35 U.S.C. 102, lack of utility; isn't that**
12:03:49 **correct?**
12:03:49 A. **102?**
12:03:54 Q. **101. Did I say 102?**
12:03:57 **THE COURT: Yes.**
12:03:58 **THE WITNESS: Yes.**
12:03:59 **BY MR. HAUG:**
12:03:59 Q. **If I did, I apologize.**
12:04:01 A. **I was confused. Sorry.**
12:04:02 Q. **Obviously, I'm confused. Let me try again.**

12:04:04 **The call for in vivo data by the examiner was in**
12:04:11 **connection with a rejection of the claims under 35 U.S.C.,**
12:04:18 **101, for lack of utility?**
12:04:21 A. **Could you say that once more? I'm sorry.**
12:04:24 Q. **What do you understand the rejection to have been?**
12:04:27 A. **The 101 rejection from the examiner I understand to**
12:04:33 **have been for lack of utility, and in particular, the lack**
12:04:37 **of provision by the applicant of in vivo data.**
12:04:42 Q. **Okay. And it is your opinion that the applicant had**
12:04:46 **data some time around 1990 or '91, and in your view, that**
12:04:54 **would have shown utility and therefore overcome this**
12:04:59 **rejection that the examiner had made. That's your view; is**
12:05:03 **that right?**
12:05:03 A. **My view is that the applicants had data as early as**
12:05:08 **July 25th, 1990, that could have overcome that objection.**
12:05:13 Q. **When you say "could have overcome," what do you mean**
12:05:16 **by that?**
12:05:16 A. **I can't read the mind of the examiner, but I do know**
12:05:24 **that these data were never presented in response to that 101**
12:05:29 **rejection.**
12:05:30 Q. **But what is your basis for saying that you believe**
12:05:36 **this data would have overcome this rejection?**
12:05:39 A. **These were in vivo data. The examiner was calling for**
12:05:43 **in vivo data. The application never contained in vivo data**
12:05:48 **until the very end, until the declaration of Scholkens that**

12:05:56 **we just talked about as part of the '018 application filed**
12:06:02 **many years later, in 1995.**
12:06:04 Q. **Are you -- do you believe the examiner was correct in**
12:06:08 **rejecting the claims in the early application for lack of**
12:06:14 **utility?**
12:06:16 A. **I'm not --**
12:06:18 **THE COURT: Do you have an objection?**
12:06:19 **MR. STULL: Yes. I object. He's asking what**
12:06:22 **the examiner thinks. We're not offering him for that.**
12:06:25 **BY MR. HAUG:**
12:06:26 Q. **My question is: Do you believe the examiner was**
12:06:28 **correct in the rejection of lack of utility in your opinion?**
12:06:32 **THE COURT: Hold on. Hold on. Doctor, hold on.**
12:06:35 **What's your objection now?**
12:06:36 **MR. STULL: He has objected that he can't**
12:06:38 **provide legal testimony and now he's asking for legal**
12:06:41 **testimony about what the examiner would have done.**
12:06:47 **MR. HAUG: This witness has said he believes**
12:06:49 **this data was responsive to a rejection and should have**
12:06:53 **been, could have been, could have been I think was his word,**
12:06:57 **could have been provided. I'm asking whether he believes**
12:06:59 **the examiner's rejection was correct.**
12:07:02 **THE COURT: Based on what?**
12:07:04 **MR. HAUG: From a scientific standpoint only.**
12:07:08 **THE COURT: Just from science?**

12:07:09 **MR. HAUG: Yes.**

12:07:09 **THE COURT: Do you still object? He's not asking for a legal opinion.**

12:07:11

12:07:14 **MR. STULL: Okay. Withdrawn.**

12:07:16 **THE COURT: You may answer.**

12:07:17 **THE WITNESS: I would have to look at the legal standards at that time to understand what the, whether the examiner was acting in a proper manner, which is how I interpret your question.**

12:07:19

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12:07:34 **BY MR. HAUG:**

12:07:34 Q. **Did you ever ask anyone whether the examiner was acting properly in preparation for your testimony here?**

12:07:37

12:07:41 A. **No.**

12:07:42 Q. **Let me ask a bit more about this period of 1991 to 1995, which you have focused on.**

12:07:51

12:07:53 **Who decided that this is the period of time that you should be looking at?**

12:08:00

12:08:01 A. **I did.**

12:08:04 Q. **And why did you pick this period of time?**

12:08:06 A. **Because as I said a few moments ago, that's when the applicants stopped responding to office actions. They responded to the very first office action, to the '162 application, and they stopped, and then it was four years later until their next response that was in 1995. So that's how I got the four years from 1991 to 1995.**

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12:08:36 Q. **You know, do you not, that the entire prosecution took**
12:08:40 **about eight years; is that right?**
12:08:42 A. **You mean from --**
12:08:48 Q. **Start to finish. From the original application**
12:08:51 **filing to the issuance of the patent, wasn't it about eight**
12:08:54 **years?**
12:08:54 A. **It is. It's from 1989 to 1997 when the patent**
12:08:58 **was --**
12:08:59 Q. **So why did you exclude the period of time between 1989**
12:09:03 **and 1991 as well as the period of time from 1995 to the**
12:09:08 **issuance in 1997?**
12:09:09 A. **I was looking at the period when the applicants were**
12:09:15 **not responding, not engaging with the Patent Office.**
12:09:18 Q. **What do you mean by not engaging with the Patent**
12:09:21 **Office?**
12:09:21 A. **When they were not responding to rejections from the**
12:09:25 **Patent Office.**
12:09:27 Q. **Dr. Raines, in the chart that you've prepared, which**
12:09:34 **is DDX-4-5, you have on there, you say, zero responses to**
12:09:42 **office action. You say that in a number of places; is that**
12:09:45 **right?**
12:09:45 A. **Yes.**
12:09:45 Q. **So is it correct that it is your understanding that**
12:09:51 **unless the applicant makes arguments that are in your view**
12:09:57 **directly responsive to what an examiner's rejection is,**

12:10:01 that's not a response?
12:10:05 A. I'm looking at these applications and looking for
12:10:11 responses, looking at the prosecution history and looking
12:10:15 for responses by the applicants to rejections from the
12:10:19 examiner and I didn't see any from 1991 to 1995.
12:10:27 Q. Is it correct that you do not consider the refilling
12:10:30 of an application a response?
12:10:33 A. As I think I said a moment ago, a lot of these
12:10:40 applications were --
12:10:41 THE COURT: Refilling of the application without
12:10:43 the data that was requested?
12:10:44 MR. HAUG: Correct.
12:10:46 THE COURT: Over and over again. Is that what
12:10:48 you are asking? Really, that's what you want to ask him?
12:10:53 MR. HAUG: I want to ask him in this chart where
12:10:55 he says zero response -- well, I want to ask him.
12:10:59 BY MR. HAUG:
12:11:00 Q. Dr. Raines, when you say zero response, you are
12:11:02 excluding the refilling of an application, aren't you?
12:11:06 A. You know, again, I'm not a patent lawyer, but when I
12:11:13 saw when I looked at this was all of these applications save
12:11:16 the last one were abandoned by the applicant and maybe they
12:11:21 filed a new application, a continuation of some sort, but
12:11:26 they didn't respond to what the examiner was calling for.
12:11:29 They had written office actions from the examiner that

clearly said, please do this. They had the ability to do that, and they didn't do that. That's what I thought.

Q. Dr. Raines, if you could turn to, in your binder, DTX-50.

THE COURT: Which binder? Which binder, Mr. Haug?

THE WITNESS: I think 50. Is that in the first one?

BY MR. HAUG:

Q. Volume 3, I believe.

A. Volume 3.

Q. Sorry.

THE COURT: Which exhibit number?

MR. HAUG: DTX-50.

THE COURT: DTX-50. Okay.

MR. HAUG: Volume 3.

THE COURT: Yes, it's here.

THE WITNESS: Okay.

BY MR. HAUG:

Q. Are you there? Okay. This is the Wirth article that we've been talking about?

A. Yes, it is.

Q. All right. And, once again, this only concerns testing of the Hoe 140 product, which is icatibant, and compares that to Stewart; is that right?

12:13:05 A. **The comparison is to a peptide that was originally**
12:13:11 **described by Stewart.**
12:13:12 Q. **And I would like you to now turn to PT -- DTX-107.**
12:13:29 **And I want --**
12:13:33 A. **Yes.**
12:13:33 Q. **Okay. You're familiar with that article?**
12:13:35 A. **Yes. This is an article again by Hoechst scientists,**
12:13:43 **including Dr. Scholkens. This article appeared in the same**
12:13:51 **issue of the British Journal of Pharmacology. It's**
12:13:54 **interesting to look at the page numbers. These were**
12:13:56 **published back to back by the Hoechst group.**
12:14:01 **This particular article by Hock talks about in**
12:14:06 **vitro assays for the icatibant peptide, and then the second**
12:14:10 **article, the so-called Wirth article, talked about in vivo**
12:14:14 **method.**
12:14:16 Q. **Thank you.**
12:14:19 **Now I would like you to turn to JTX-6, which**
12:14:24 **would be in Volume 2. JTX-6.**
12:14:34 A. **That's --**
12:14:35 Q. **6A I think is a clearer copy. Are you there?**
12:14:57 A. **No. I'm sorry. It's a challenge.**
12:15:16 Q. **Now, if you could turn to JTX 6A.221.**
12:15:39 A. **Yes.**
12:15:40 Q. **Okay. And this is the, this is the application that**
12:15:44 **was filed February 19, 1991, isn't it?**

12:15:48 A. **You said February 19th?**

12:15:58 Q. **Well, is that -- whatever that date is in the upper left.**

12:16:01 A. **Oh, I see. Yes. Yes. It confused me because I guess it was received February 25th.**

12:16:05 Q. **Okay. And you're familiar with this document; is that right?**

12:16:07 A. **I believe I've seen this before.**

12:16:10 Q. **Okay. And if you would turn -- well, this is responding to an office action dated August 17, 1990. I'm reading from the first line of the amendment on Page 221, 221.**

12:16:14 **Are you with me?**

12:16:18 A. **Yes.**

12:16:23 Q. **All right. In response to the office action dated August 17, 1990. And it goes on to talk -- if we go to the next page, about halfway down. It says, "Please delete claims 1 to 4 and replace them with new claims 7 to 13."**

12:16:29 **Do you see that?**

12:16:30 A. **Which page are you on?**

12:16:31 Q. **I'm on Page 222.**

12:16:34 A. **It says, delete Claim 1 and insert therefore Claim 10.**

12:16:40 Q. **I'm in the middle.**

12:16:45 A. **Oh, I see.**

12:16:49 Q. **Very good. So they were deleting some claims and**

12:16:50

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12:17:07

12:17:10

12:17:12

12:17:15 **adding new claims; is that correct?**

12:17:16 A. **That is correct.**

12:17:17 Q. **All right. And if we go -- and this is in response to the office action where the examiner said, claims were rejected for lack of utility; isn't that right?**

12:17:29 A. **I can't agree with that.**

12:17:33 Q. **You can't agree with that?**

12:17:35 A. **No.**

12:17:35 Q. **You don't know?**

12:17:36 A. **No. I can't agree with that.**

12:17:38 Q. **All right. Let me try this a different way. Let me see if I can get the office action.**

12:17:53 **The examiner rejected all the claims for lack of utility; is that correct?**

12:17:56 A. **In which application?**

12:18:01 Q. **Do you remember which one?**

12:18:02 A. **Are you referring to the '162 application?**

12:18:07 Q. **Yes.**

12:18:08 A. **I know the examiner rejected claims for lack of utility.**

12:18:14 Q. **If you go to 6.152, please.**

12:18:28 A. **Six -- this is in tab JTX-6?**

12:18:32 Q. **Right.**

12:18:33 A. **At page --**

12:18:34 Q. **Still JTX-6.**

12:18:37 A. **152?**

12:18:39 Q. **152, please.**

12:18:40 A. **Yes.**

12:18:41 Q. **All right?**

12:18:45 A. **Yes.**

12:18:45 Q. **Do you see in the upper right-hand corner it says, 8/17/1990. Do you agree with me this is an office action of that date?**

12:18:52

12:18:54 A. **Yes. This is the first office action for the '162 application.**

12:18:58

12:18:59 Q. **And you see down below it says, claims 1 to 6 are pending, and then if we go down to the fourth line, claims 1 to 6 are rejected.**

12:19:03

12:19:06

12:19:09 A. **I see that.**

12:19:10 Q. **Okay. Going back to JTX 6A.221, this is responding to that office action.**

12:19:20

12:19:21 **Do you follow me?**

12:19:22 A. **I can't agree with that.**

12:19:24 Q. **All right. And why can't you agree with that?**

12:19:30 A. **Well, this is a -- the -- what was done to go into the '149 application, so to file the continuation, they added this data, as I understand.**

12:19:42

12:19:46

12:19:55 **And can you show me --**

12:19:57 **THE COURT: What do you want to say?**

12:19:58 **BY MR. HAUG:**

12:19:59 Q. **Which one do you want?**

12:20:00 A. **The second page. I'm on 152 and now you're on -- what was the other page? Two? 221?**

12:20:04 **THE COURT: Yes.**

12:20:09 **THE WITNESS: Yes. So this amendment -- they are adding, if I recall, they're adding some change in the claims and adding some data that, in which they are seeking to address the office action to the '162 application.**

12:20:17 **BY MR. HAUG:**

12:20:19 Q. **I would like to turn your attention to JTX-6A.233.**

12:20:29 A. **Yes.**

12:20:35 Q. **Okay. And you see near the top under the indented paragraph, it says, see MPEP section 608.01 (p).**

12:20:46 **Do you see that?**

12:20:48 A. **I see that.**

12:20:55 Q. **Do you know what that is?**

12:20:55 A. **What MPEP stands for?**

12:21:02 Q. **Correct.**

12:21:10 A. **I don't know.**

12:21:12 Q. **So you don't know what this section of the MPEP said?**

12:21:13 A. **I'm not -- I'm not familiar with what MPEP means.**

12:21:14 Q. **All right. I would like to now turn to PTX-72, please. PTX-72. This is also on line 3.**

12:21:16 **THE COURT: PTX-72?.**

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12:22:02

12:22:04 **MR. HAUG: Yes.**

12:22:05 **THE COURT: Which line? You gave us three**
12:22:07 **lines.**

12:22:11 **MR. HAUG: Line 3 to 4.**

12:22:12 **THE COURT: Line 3?**

12:22:13 **MR. HAUG: Yes.**

12:22:14 **THE COURT: All right. What page did you say?**
12:22:38 **I'm sorry.**

12:22:39 **MR. HAUG: I was going to 72.2. I take it back.**
12:22:47 **Let's start with the first page, 72.1, the first page.**

12:22:52 **BY MR. HAUG:**

12:22:53 Q. **72.1. Let me know when you are there, Dr. Raines.**

12:22:56 A. **I'm there.**

12:22:58 Q. **All right. Do you see in the upper right-hand corner**
12:23:01 **it says 608.01?**

12:23:03 A. **I do.**

12:23:04 Q. **And we're a ways down on the right-hand column. It**
12:23:08 **says, guidelines for considering disclosures of utility in**
12:23:12 **drug cases?**

12:23:16 A. **I do.**

12:23:17 Q. **Have you ever seen this before?**

12:23:19 A. **Perhaps, but I can't be sure.**

12:23:26 Q. **And if we go to 72.2, please. And the first paragraph**
12:23:35 **in the right-hand column, it says, proof of utility under**
12:23:39 **this section may be established by clinical or in vivo or in**

12:23:45 vitro data, or combinations of these, which would be
12:23:49 convincing to those skilled in the art.
12:23:51 Did I read that correctly?
12:23:53 A. Yes, you did.
12:23:56 Q. But you're not aware of this utility guideline in the
12:24:02 manual of patent examining procedure, are you?
12:24:04 A. I know there's debate about in vivo and in vitro data,
12:24:15 but I am not a patent lawyer.
12:24:18 Q. And the date of this, if we look at the lower
12:24:23 right-hand corner, it says May 1988.
12:24:26 Do you see that?
12:24:27 A. I do see that.
12:24:28 Q. Dr. Raines, I'd like you to turn to JTX-6A.1
12:24:57 A. Which volume is that in?
12:25:01 Q. Six. That would be in Volume 2, 2 of 4.
12:25:17 THE COURT: What is the exhibit number?
12:25:19 MR. HAUG: PTX-6. JTX-6. Sorry. JTX-6.
12:25:30 THE WITNESS: I'm there.
12:25:31 BY MR. HAUG:
12:25:31 Q. Okay. I will wait for you. JTX-06A.1. And do you
12:25:40 recognize this document?
12:25:41 A. So this is the prosecution history for the '162, '149
12:25:48 and '052 applications.
12:25:53 Q. And please point to JTX 6A.121 within that
12:25:58 application.

12:26:17 A. **Yes.**

12:26:17 Q. **These are the claims that were filed in the original application, aren't they?**

12:26:22 A. **These are the Group 1 applications.**

12:26:23 Q. **All right. And Claim 1, for example, is directed to a genus of compounds.**

12:26:25 **Do you agree with that?**

12:26:29 A. **Yes.**

12:26:30 Q. **And that genus of compounds covers many, many compounds; is that right?**

12:26:31 A. **Yes.**

12:26:32 Q. **Perhaps thousands?**

12:26:36 A. **Perhaps millions.**

12:26:38 Q. **Perhaps millions. Okay.**

12:26:38 **And I would like -- I would like you now to turn to Page 152. Actually, I had another question. When you were looking at the original claims, were any of the original claims directed to icatibant only?**

12:26:40 A. **Not that I recall.**

12:26:42 Q. **Okay. So if we then go to Page 152, please.**

12:26:44 A. **Yes. I'm there.**

12:26:51 Q. **And this is the office action we've been looking at; is that right?**

12:27:00 A. **This is the first office action for the '162 patent application.**

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12:27:33 Q. **And claims 1 to 6, the ones we just looked at, were all rejected in this office action; is that right?**

12:27:36 A. **We just looked at Claim 1, but it says here that all claims, 1 through 6, are rejected.**

12:27:39 Q. **Okay. And please go to Page 153.**

12:27:44 A. **Yes.**

12:27:46 Q. **And if you go down to the last paragraph, it says, applicant's election of peptide specie of structure as shown on Page 31, Example 59 in Paper Number 1, is acknowledged.**

12:27:55 **What do you understand the examiner to be saying there?**

12:27:56 A. **So my understanding of this is that there was a restriction requirement, and the applicants were asked to choose a particular sequence for examination and that the application would be examined through the lens of that sequence, and they were selecting Example 59.**

12:28:00 Q. **Okay. And if we go to Page 154, still in JTX-6. And near the top it says, right below the indent: Claims 1 to 6 are rejected under 35 U.S.C. 101 because the invention as disclosed is inoperative and therefore lacks utility.**

12:28:04 **Do you see that?**

12:28:07 A. **I do see that.**

12:28:10 Q. **And that's the rejection that you have been focused on; isn't that correct?**

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12:29:16 A. **Yes, and the examiner goes on to describe in the**
12:29:23 **subsequent paragraph the meaning that she has for, the**
12:29:28 **underlying basis for that rejection.**
12:29:30 Q. **Correct. And it is your testimony that the applicant**
12:29:36 **had some data that in your view from a scientific point of**
12:29:40 **view would be responsive to showing utility for icatibant;**
12:29:46 **isn't that correct?**
12:29:46 A. **Yes, as of July 25th, 1990, the applicant had in vivo**
12:29:53 **data that would have, or at least could have been responsive**
12:29:57 **to this rejection, but did not put it forth.**
12:30:02 Q. **But this rejection is not based on a claim to**
12:30:05 **icatibant; isn't that right?**
12:30:07 A. **Icatibant is included in the claims of this**
12:30:15 **application.**
12:30:16 Q. **But claims 1 to 6 don't call out icatibant, and as you**
12:30:21 **just testified a little while ago, cover maybe thousands, or**
12:30:24 **even millions of compounds; isn't that right?**
12:30:26 A. **Claims 1 through 6 are large genus claims, but one of**
12:30:32 **the species is icatibant.**
12:30:34 Q. **But --**
12:30:36 **THE COURT: Mr. Haug, we're going to take lunch.**
12:30:38 **Be back in an hour.**
12:30:39 **MR. HAUG: Certainly. Thank you, Your Honor.**
12:30:50 **(Luncheon recess taken.)**
11:38:55 **THE COURT: Please, take your seats. Doctor,**

please return to the stand.

All right. Doctor, good afternoon.

THE WITNESS: Good afternoon.

MR. BLUMENFELD: Your Honor, Mr. Haug stepped out just as you were coming in coincidentally. He will be back shortly. Sorry about that.

(Pause.)

BY MR. HAUG:

Q. Good afternoon again, Dr. Raines.

I think before the break we were looking at JTX-6, and I would like to direct you to 6.152. Are you with me, 152?

A. I am there.

Q. This is the office action we have been speaking about. Right?

A. This is the office action for the '162 application.

Q. If you would please turn to 154, two pages into the document?

A. Yes.

Q. You see here where Claims 1 to 6 are rejected under 35 U.S.C. 101 because the invention as disclosed is nonoperative and therefore lacks utility.

Right?

A. I see that.

Q. This utility rejection is to all of the Claims 1

13:33:26 through 6, which are genus claims. Isn't that correct?
13:33:32 A. It's to Claims 1 to 6. I don't recall if they are all
13:33:35 genus claims, if you tell me...
13:33:40 Q. So if you turn to JTX-6.221, please, let me know when
13:34:03 you get there?
13:34:03 A. Yes.
13:34:04 Q. This is the amendment and response to this office
13:34:07 action we just looked at. Correct?
13:34:10 A. Right. This is the response to the office action for
13:34:12 the '162 application, yes.
13:34:14 Q. Thank you. And if we look to the next page, 222, you
13:34:26 see where it says in the claims, "Please amend Claims 5 to 6
13:34:30 as follows." And then below it that it says, "Please delete
13:34:35 Claims 1 to 4 and replace them with new Claims 7 to 13."
13:34:40 A. Yes.
13:34:40 Q. Then they set forth the claims and just looking at
13:34:44 Claim 7 very quickly, that is a genus claim, isn't it?
13:34:50 A. Claim 7 seems to be a genus claim with a number of
13:34:54 species, yes.
13:34:55 Q. And I would like you now to look at Claim 13, and
13:35:08 that's icatibant, isn't it?
13:35:12 A. Claim 13?
13:35:13 Q. Which is being added here?
13:35:15 A. Can you point to a page?
13:35:17 Q. Certainly. That would be on Page 229.

13:35:24 A. **Claim 13, yes.**

13:35:35 Q. **If you would now turn to Page 231. At the bottom, the last paragraph, it starts, "The examiner has rejected Claims 1 to 6 under 35 U.S.C. 101, asserting that the invention as disclosed is nonoperative and therefore lacks utility," then it goes on. Right? It goes on until Page 233, if you could move to that page, please?**

13:36:08 A. **233, yes.**

13:36:09 Q. **Up at the top it says, "Applicants respectfully note that: [proof] of utility under 608.01 may be established by clinical or in vivo or in vitro data, or combinations of these, which would be convincing to those skilled in the art [and] animal tests may be adequate where the art would accept these as appropriately correlated with human utility."**

13:36:36 **Did I read that correctly?**

13:36:37 A. **You did.**

13:36:37 Q. **Right before that, after it says MPEP 608.01, they go on to say, "Applicants respectfully submit that the in vitro data of the instant specification is in accord with accepted methods of establishing utility by in vitro testing of bradykinin antagonist action using the modeling disclosed in the specification at Page 17, Lines 7 to 13."**

13:37:10 **Did you consider this argument that the applicants were making in response to the 101 rejection?**

13:37:20 A. **I did read this before.**

13:37:22 Q. **So the applicants here are saying, we don't need to put in in vivo data; in vitro data, which we already have in the application, should be sufficient. Isn't that what they are arguing here?**

13:37:33 A. **The applicants are making that argument.**

13:37:35 Q. **I would like you to move on to 247, please. Are you with me?**

13:37:54 A. **I am.**

13:37:55 Q. **This is the next office action, is it not?**

13:37:57 A. **Yes. This is the second and final office action for the '162 application.**

13:38:03 Q. **This is an examiner's office action dated May 31, 1991?**

13:38:08 A. **That's correct.**

13:38:08 Q. **And if we go down, the cover page to No. 3 says "Claim 13 is allowed."**

13:38:17 **Do you see that?**

13:38:18 A. **I do see that.**

13:38:19 Q. **Do you see it on the cover page?**

13:38:22 A. **Yes.**

13:38:23 Q. **I have it highlighted?**

13:38:24 A. **Yes.**

13:38:24 Q. **Claim 13 is directed to icatibant. Right?**

13:38:30 A. **I believe that's the claim we just covered.**

13:38:33 Q. **It is the one I just showed you?**

13:38:36 A. **Yes.**

13:38:36 Q. **Right below that it says "Claims 5 to 12 are rejected."**

13:38:42 A. **Yes.**

13:38:42 Q. **If we move to the next page, 248, if we go under the indent there, it says, "Claims 5 to 12 are rejected under 35 U.S.C. 101 because of the reasons set forth at Pages 3 and 4 of the last office action, 8/17/90."**

13:38:43 **Do you see that?**

13:38:51 A. **I do see that.**

13:38:56 Q. **Would you agree with me that the examiner is rejecting Claims 5 to 12 but not Claim 13 to icatibant?**

13:39:00 A. **That's true in this sentence, yes.**

13:39:05 Q. **So, Dr. Raines, if the examiner here has dropped the rejection of Claim 13 over lack of utility, do you still believe they needed to submit scientific data from the Wirth article?**

13:39:06 A. **My understanding about this office action -- and I would have to read through the entire office action -- is that although the cover sheet claimed that Claim 13 was allowed, that the text of the documents did not allow Claim 13.**

13:39:07 Q. **Let me maybe help you with that, if we go to Page 253 in this office action. Right at the top, it says, "Claims 5**

13:40:32 **to 13 are rejected under 35 U.S.C. 103."**

13:40:36 **Do you see that?**

13:40:37 A. **Yes.**

13:40:37 Q. **So you would agree with me, right, that all the Claims 5 to 13 are being rejected under 103 at this portion of the office action. Right?**

13:40:48 A. **I see that.**

13:41:06 Q. **I would like you now to please stay with JTX-6A. And if we could go to 468, please. Do you recognize this?**

13:41:36 A. **468 is the office action for the '149 application.**

13:41:41 Q. **It has a date of July 1, '92 in the upper right. Is that correct?**

13:41:46 A. **Yes.**

13:41:46 Q. **And on this cover page it says Claims 5 to 17 are rejected. Right?**

13:41:53 A. **Yes, it does.**

13:41:54 Q. **Please turn to Page 476. Do you see about halfway down the page it says, "Claims 5 to 17 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter"?**

13:42:20 **"The claimed invention is identical to the reference compound and method published in the British Journal, Pharmacological Journal, Hock, et al., or Wirth et al., coauthored by some of the present inventors."**

13:42:38 **Do you see that?**

13:42:39 A. **I do.**

13:42:39 Q. **Do you understand what the examiner is saying here by rejecting Claims 5 to 17 under 35 U.S.C. 102(f)?**

13:42:48 A. **My understanding of this is that this is an inventorship rejection. The examiner is concerned that there is information in the -- here in the public domain available to her that the inventors of the application may not include all the inventors of the application.**

13:43:19 Q. **And in the second sentence that I read, the examiner here is citing the Wirth article that you have been testifying about. Isn't she?**

13:43:30 A. **She is citing this in the context of the 102(f) rejection.**

13:43:35 Q. **Well, as of the date of this office action, which was July, July 1st, 1992, the Wirth article that you have been focused on is now of record in the patent file history, isn't that correct?**

13:43:53 A. **I am not sure how the -- I am not sure about the words "of record." But the Wirth article is cited here in this paragraph about the 102(f) rejection.**

13:44:25 Q. **Dr. Raines, I would like you to now go to JTX-7, please. 7A, would you say please turn to Page 263. Let me know when you're there?**

13:45:08 A. **Yes.**

13:45:09 Q. **And this is the June 6, 1995 response by the**

13:45:16 applicants to the office action which you testified about
13:45:20 earlier, isn't it?
13:45:22 A. Yes. This is in response to the '018 application.
13:45:29 Q. If you would please turn to Page 298?
13:45:38 A. Yes.
13:45:38 Q. And this, about halfway down the page it says
13:45:46 "Rejection under 35 U.S.C. 101."
13:45:49 Do you see that?
13:45:51 A. I do.
13:45:51 Q. And then following, there is argument, if I can put it
13:45:56 that way, about the rejection that the examiner had made,
13:46:00 and it goes on for a little bit. Right?
13:46:07 A. Yes.
13:46:08 Q. If we could turn now to Page 301, please?
13:46:16 A. Yes.
13:46:18 Q. The first paragraph. It says, "In further support of
13:46:22 the utility, applicants submit copies of the following
13:46:26 publications that attest to the utility of the claimed
13:46:30 bradykinin antagonists in treating a variety of pathological
13:46:34 states mediated by bradykinin."
13:46:38 And then it goes on to cite, the applicants are
13:46:46 citing as many as eight references. Is that correct? I am
13:46:55 still on Page 301.
13:46:57 A. Eight, yes.
13:46:59 Q. Okay. You agree with me. And the Wirth 1990 or '91

13:47:06 **article that you have been testifying about is not among**
13:47:08 **these articles, is it?**
13:47:12 A. **Well, the Wirth article is not in this list. It is in**
13:47:16 **the declaration of Dr. Scholkens that is also part of this**
13:47:22 **response.**
13:47:22 Q. **That's correct. But it's not set forth here in the**
13:47:26 **Remarks section by applicants, is it?**
13:47:30 A. **It's not in this list. But it is part of the response**
13:47:34 **of the applicants.**
13:47:35 Q. **And am I correct to note that some of these articles,**
13:47:39 **like, for example, the first Wirth article is 1993, there is**
13:47:45 **a next one, 1994, and there are a number of other 1994**
13:47:51 **articles. Do you see that?**
13:47:52 A. **I do see that. We talked earlier about the 1993**
13:47:56 **article, which was submitted in 1992.**
13:48:03 Q. **But you would agree, would you not, that in this**
13:48:06 **particular response by the applicants, they are citing a**
13:48:09 **number of publications to the examiner in connection with**
13:48:14 **the utility rejection. Would you agree with that?**
13:48:21 A. **They are citing these papers in that sense, yes.**
13:48:24 Q. **Dr. Raines, please turn to JTX-7, again, and Page 263.**
13:48:54 **We are still in the same response, I think. Page 263.**
13:49:02 A. **Okay.**
13:49:02 Q. **We are in that response. I would like you to go to**
13:49:13 **Page 299.**

13:49:23 A. **I am there.**

13:49:24 Q. **The first full paragraph, "According the Guidelines for Examination of Applications for Compliance with Utility Requirement (Fed. Reg., Vol 60, Page 98), [a] rejection under Section 101 should not be maintained if an asserted utility for the claimed invention would be considered credible by a person of ordinary skill in the art in view of all evidence of record.'**

13:49:56 **"Applicants submit that the utility of the claimed invention would be considered credible by one of ordinary skill in the art on the basis of the specification alone."**

13:50:04 **Did I read that correctly?**

13:50:06 A. **Yes.**

13:50:06 Q. **Are you familiar with the guidance for examination of applications for compliance with the utility requirement as referenced in Fed. Reg. Volume 6 or not?**

13:50:16 A. **I do not believe I have read that.**

13:50:17 Q. **You never looked at that. At any time in your work on this case?**

13:50:22 A. **I don't know. I can't recall.**

13:50:37 Q. **Please turn to PTX-73, Volume 3 of 4, PTX-73.**

13:51:13 A. **I was in Volume 2, sorry.**

13:51:16 Q. **PTX-73. Do you recognize this document, which is from the Federal Register Utility Guidelines?**

13:51:52 A. **I may have seen this before, but I am not especially familiar with it.**

13:51:56 Q. **Dr. Raines, you testified about Nova and some of the compounds that Nova was working under. Do you recall that?**

13:52:11 A. **Yes.**

13:52:11 Q. **Other than looking at publications from Nova or about Nova compounds which you did testify about, do you have any other experience with anything that Nova did at any time?**

13:52:29 A. **No. I reviewed several publications from Nova scientists by bradykinin antagonists, publications from the early 1990s. But I am not aware of other information.**

13:52:52 **MR. HAUG: Your Honor, may I just consult with Mr. Blumenfeld?**

13:52:54 **THE COURT: Yes.**

13:52:57 **(Pause.)**

13:53:07 **MR. HAUG: No further questions, Your Honor.**

13:53:08 **THE COURT: Redirect.**

13:53:15 **REDIRECT EXAMINATION**

13:53:15 **BY MR. STULL:**

13:53:28 Q. **Would you look at JTX-6A, Tab F?**

13:53:54 A. **Which tab?**

13:53:55 Q. **Tab F, please?**

13:53:56 A. **Yes.**

13:53:57 Q. **Is Tab F the February 15th, 1991 response you were asked some questions about?**

13:54:10

13:54:12 A. **Yes, this is the response to the office action for the '162 application.**

13:54:20 Q. **Can we go to Page 233 of JTX-6A in this response. If you could go right to where it says "See MPEP."**

13:54:22 **Do you recall you were asked some questions about this MPEP statute right here?**

13:54:31 A. **Yes.**

13:54:36 Q. **Can we look at DDX4.9. Dr. Raines, did you include the February 19th, 1991 response we just looked at as part of the period of delay in this slide?**

13:54:37 A. **My period of delay started at May 31st, 1991, not February 19th, 1991. So, no.**

13:54:41 Q. **Can you turn to Tab G of JTX -- I think it's JTX-7A.**

13:54:41 A. **Yes.**

13:55:00 Q. **And is there the June 6, 1995 response you were asked some questions about?**

13:55:05 A. **Yes.**

13:55:10 Q. **And if we could go to Page 299. And if you go to the top where it says, according.**

13:55:15 **Do you recall some questions you were asked about these guidelines, Fed. Reg Volume 60, Page 98?**

13:55:22 A. **I do.**

13:55:32 Q. **And if we could go back to DDX4-9. Do you include any time period after the June 6th, 1995 response that included that Fed. Reg statute in your period of delay?**

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13:56:13 A. **No.**

13:56:17 Q. **Okay. Could you turn to Tab H, the Scholkens declaration. Excuse me. I guess that's Tab H in JTX-7A to be precise. And if we can go to Paragraph 5.**

13:56:34 **Are you at Paragraph 5?**

13:56:41 A. **Yes, I'm there.**

13:56:42 Q. **Okay. Is this the first time that applicant cited Wirth 1991 in response to a 101 rejection?**

13:56:53 A. **Yes, it is.**

13:57:02 **MR. STULL: No more questions.**

13:57:03 **THE COURT: Thank you, Doctor. Please be careful stepping down. They'll get it.**

13:57:06 **THE WITNESS: They'll get it?**

13:57:07 **THE COURT: Yes, they will. Right now. All right.**

13:57:10 **(Witness excused.)**

13:57:43 **MR. HAUG: Your Honor, shall we clean up?**

13:57:45 **THE COURT: Yes. Absolutely.**

13:58:13 **MR. HAUG: Your Honor, with the testimony of Dr. Raines, the defendants rest their case-in-chief. We have rebuttal witnesses for probably Friday, but that's our case-in-chief.**

13:58:20 **THE COURT: All right.**

13:58:24 **MR. HAUG: Your Honor, I would like to very briefly, very briefly make a motion under Rule 52(c) on one**

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13:58:35 **point only, and that is the complete failure to present any**
13:58:39 **evidence with respect to intervening rights and prejudice**
13:58:43 **during the period of delay, which is clearly required by the**
13:58:48 **Cancer Research case, which applies here to this case.**
13:58:51 **Putting aside all questions of fact that may be**
13:58:54 **involved with the patent prosecution, it is what it is, it**
13:58:58 **is a necessary element under the Cancer Research case and**
13:59:02 **Supreme Court precedent that there has to be, has to be a**
13:59:07 **showing of clear and convincing evidence, of intervening**
13:59:13 **rights and prejudice.**
13:59:13 **We heard testimony from Dr. Burch about Nova.**
13:59:18 **We saw some articles about Nova and they were working on**
13:59:22 **some compounds. That's fine. However, there's no prejudice**
13:59:26 **to Nova. The testimony is clear, they abandoned the**
13:59:29 **project, they never went forward with the project, and there**
13:59:32 **is no analysis that has ever come forward with regard to**
13:59:36 **prejudice, no one. And the period of delay, alleged delay,**
13:59:40 **is 1991 to 1995. And Fresenius here didn't even file the**
13:59:44 **ANDA until obviously much, much later, 19 years later. And**
13:59:47 **there's no proof. There's no proof whatsoever I believe in**
13:59:50 **this regard about prejudice, a necessary element of patent**
13:59:54 **prosecution, laches.**
13:59:57 **And while I think as a matter of law that's the**
14:00:02 **case, and we would like to avoid, if we can, having to walk**
14:00:07 **through the file history again in our case, which really we**

14:00:12 **think shouldn't be necessary because they have not satisfied**
14:00:15 **this prong, which they cannot get past, they cannot get**
14:00:19 **around this prong. There's no intervening prejudicial**
14:00:22 **rights. Thank you.**
14:00:23 **THE COURT: Mr. Wiesen?**
14:00:25 **MR. WIESEN: Thank you, Your Honor.**
14:00:27 **Respectfully, I think that they're misreading the**
14:00:30 **requirement in Cancer Research for how prejudice is defined.**
14:00:34 **The Federal Circuit was quite clear that in providing a**
14:00:37 **definition of how one proves prejudice for prosecution**
14:00:42 **laches, and what they say is, proof that somebody was**
14:00:44 **working in the space at the time, during the period of**
14:00:48 **delay.**
14:00:48 **The evidence is at least at this point even**
14:00:51 **undisputed that that has happened. Nova was working in the**
14:00:54 **space on compounds that were covered, and based under the**
14:00:58 **Cancer Research standard, the definition of prejudice the**
14:01:02 **Federal Circuit provided, we've carried the burden.**
14:01:07 **The second argument we have is that while Mr.**
14:01:09 **Haug is certainly right that the reference in Cancer**
14:01:12 **Research is to people who are prejudiced during the period**
14:01:14 **of delay, there is a second argument that was made and**
14:01:18 **rejected, but rejected factually in Cancer Research, and**
14:01:22 **that were distinguishable.**
14:01:23 **The undisputed facts that we've stipulated to,**

14:01:27 so they are in the record for purposes of the Rule 52(c)
14:01:30 motion, are that Firazyr filed on the NCE minus one date and
14:01:36 Shire got it by the patent term extension. And the Federal
14:01:40 Circuit in Cancer Research rejected the prejudice to the
14:01:45 generic defendant when neither of those issues were held.
14:01:49 Here, with those two facts in the record,
14:01:52 legally, that's sufficient for prejudice to Firazyr, and we
14:01:57 would ask you to deny the 52(c) motion.
14:01:59 THE COURT: All right. I'm going to reserve on
14:02:01 the motion. Frankly, this is not an issue that I have a
14:02:06 great deal of competency with yet. I hadn't read the cases.
14:02:10 I have not had time to read them. I will and see whose
14:02:14 interpretation I agree with. Both lawyers are interpreting
14:02:17 the same case differently.
14:02:19 Mr. Haug, let's go.
14:02:21 MR. HAUG: Thank you, Your Honor. Plaintiffs
14:02:25 begin their case by calling their first witness, Dr. Kaplan.
14:02:30 Mr. Blumenfeld will conduct the examination.
14:02:42 PLAINTIFF'S TESTIMONY
14:02:43 ... ALLEN P. KAPLAN, having been
14:02:55 duly sworn as a witness, was examined and testified as
14:02:58 follows ...
14:03:04 THE COURT: Good afternoon, Doctor.
14:03:07 Do you have some binders, Mr. Blumenfeld?
14:03:10 MR. BLUMENFELD: Thank you, Your Honor. Can I

14:03:13 **distribute some notebooks and a bottle of water for the**
14:03:16 **witness?**
14:03:16 **THE COURT: Please do.**
14:03:18 **MR. BLUMENFELD: Thank you.**
14:03:18 **(Mr. Blumenfeld handed binders to the Court and**
14:03:22 **to the witness.)**
14:03:36 **THE WITNESS: Thank you.**
14:03:45 **DIRECT EXAMINATION**
14:03:46 **BY MR. BLUMENFELD:**
14:03:54 Q. **Good afternoon, Dr. Kaplan.**
14:03:56 A. **Hi.**
14:03:58 Q. **Are you a medical doctor?**
14:04:00 A. **I am.**
14:04:00 Q. **Can we turn to PTX-176. It is in your book. We'll**
14:04:11 **put it on the screen also.**
14:04:15 **Is PTX-176 your CV, Dr. Kaplan?**
14:04:19 A. **It is.**
14:04:19 Q. **And does it include your educational and professional**
14:04:22 **background?**
14:04:23 A. **Right.**
14:04:24 Q. **We'll get into some of the issues on there. Before we**
14:04:28 **do, can you tell us where you work currently?**
14:04:31 A. **Yes. I'm a Clinical Professor of Medicine at the**
14:04:34 **Medical University of South Carolina.**
14:04:36 Q. **And in any particular division?**

14:04:39 A. **Yes. The Division of Pulmonary Disease and Critical**
14:04:44 **Care Medicine.**
14:04:45 Q. **Okay. Have you prepared some demonstrative exhibits**
14:04:49 **to use during your testimony?**
14:04:50 A. **Yes, I did.**
14:04:51 Q. **And if we could put those up. Let's turn to**
14:04:54 **Demonstrative 2.1.**
14:05:00 **And can you tell us what's shown on**
14:05:01 **Demonstrative 2.1?**
14:05:02 A. **Yes. The first item on the upper left is where it**
14:05:06 **states my education. So I'm a graduate of Columbia**
14:05:10 **University in 1961. I was a chemistry concentrate.**
14:05:16 **Graduated magna cum laude, then went to medical school.**
14:05:20 **That was at Downstate Medical School, which is in Brooklyn,**
14:05:24 **New York. Graduated summa cum laude in 1965.**
14:05:28 Q. **And after your medical school education, can you**
14:05:30 **describe briefly your practice as a physician?**
14:05:36 A. **Sure. That is a little bit later in the same chart.**
14:05:40 **I was an intern and resident at the University of Rochester**
14:05:44 **in Rochester, New York.**
14:05:46 **From there I went to the National**
14:05:50 **Institutes of Health, where I was a clinical associate in**
14:05:55 **the arthritis and metabolic diseases division.**
14:05:59 **After leaving the NIH, I did a second**
14:06:01 **specialty. At NIH it was rheumatology. I became an**

14:06:05 **allergist and immunologist at Harvard, at the Robert B.**
14:06:11 **Brigham Hospital from 1969 to '72.**
14:06:13 **I returned to the NIH after my fellowship.**
14:06:15 **I was appointed head of allergic diseases there. I remained**
14:06:21 **from '72 to '78. I then was a Professor of Medicine at the**
14:06:27 **State University of New York at Stony Brook.**
14:06:30 **Half my time I was a division head in**
14:06:32 **allergy, rheumatology and clinical immunology. The other**
14:06:35 **half I was chairman of the department of medicine. After**
14:06:38 **leaving Stony Brook, I came to South Carolina, to my present**
14:06:42 **position at the Medical University of South Carolina. I've**
14:06:48 **been there 21 years.**
14:06:49 Q. **During all of this time have you have you had**
14:06:53 **experience in treating hereditary angioedema?**
14:06:58 A. **I first encountered heredity angioedema in my**
14:07:01 **fellowship at Harvard so it's roughly 1970. Since that time**
14:07:06 **regardless of which place I was at, I always encountered**
14:07:09 **patients with hereditary angioedema. I was either,**
14:07:14 **depending upon the circumstances, sent the patients in**
14:07:16 **consultation because it was known that this was an area of**
14:07:20 **particular expertise of mine, or just by luck that people in**
14:07:24 **the community who presented with angioedema, some of which**
14:07:29 **turned out to have the hereditary type.**
14:07:31 Q. **Do you still treat patients with hereditary**
14:07:35 **angioedema?**

14:07:35 A. **I do not. I retired from clinical practice, it's**
14:07:39 **about eight to nine years ago, and continued doing medical**
14:07:42 **research and teaching.**
14:07:43 Q. **Do you still lecture on the subject of treatment of**
14:07:47 **hereditary angioedema?**
14:07:48 A. **Oh, yes. I lecture broadly on allergy and clinical**
14:07:54 **immunology but the most frequent requests are for urticaria,**
14:07:59 **which is hives, or angioedema, and particularly hereditary**
14:08:03 **angioedema, and that occurs throughout the United States,**
14:08:07 **sometimes internationally at conferences.**
14:08:08 Q. **And do you have a lecture that's upcoming?**
14:08:11 A. **Indeed. The next one will be in March of this year.**
14:08:15 **There's a joint meeting of the American academy of allergy**
14:08:20 **and world allergy in Orlando. I'm giving two presentations**
14:08:24 **at that meeting and they are both -- they both relate to**
14:08:27 **HAE. One is on pathogenesis and one is entitled how a C1**
14:08:34 **inhibitor works.**
14:08:34 Q. **Have you taught to the subject of hereditary**
14:08:36 **angioedema?**
14:08:37 A. **Yes, indeed, at all of the various stops that were**
14:08:40 **listed, I teach at the medical centers. The focus is on**
14:08:46 **immunology and allergy and among the lectures are angioedema**
14:08:55 **and particularly HAE.**
14:08:56 Q. **Have you done research on the subject of hereditary**
14:09:00 **angioedema?**

14:09:00 A. **Indeed.**

14:09:01 Q. **Can you tell us a little bit about that?**

14:09:04 A. **Yes. That's perhaps a combination, if you will, but my publication record is about 350 total. A little over a hundred of those deal with bradykinin, either the mechanism by which bradykinin is formed in the human body or degraded in the human body. About 30 of those articles deal with angioedema more specifically, and of those, 25 would be directly related to hereditary angioedema. That means those last 25 not so much in vitro work, but we were really working with the patients and making determinations where the patient was part of the project.**

14:09:44 Q. **Okay. I've put up PDX-2.2 and on the right side there are a number of publications. And do those involve hereditary angioedema?**

14:09:57 A. **Those are excerpted from my CV. They're among those involving HAE. The first one, and I put it first. It was to call attention. It's particularly important because this Fields article, this is the article in which we were the first to show that bradykinin, which, of course, is one of the main subjects today, that bradykinin is the molecule that causes the swelling we see in hereditary angioedema, and that discovery was made in 1983.**

14:10:27 Q. **And is that Fields article in your notebook as PTX-191?**

14:10:32 A. **Yes, it is.**

14:10:37 Q. **Okay. And in addition to that, I just wanted to ask you a little bit about one other article that you wrote. And turn to PTX-179. Is that the second, the second publication listed on the demonstrative exhibit?**

14:10:54 A. **Yes, it is. That's a review article in 1988, so it's prior to many of the current medications for hereditary angioedema, prior to any of them being around. I guess it's the year before the patent in question, and we had reviewed the state of the art at that point in time.**

14:11:17 Q. **Did your review of the state of the art in this article include, you can see it at the bottom of the second column, the treatment of acute attacks?**

14:11:26 A. **Indeed.**

14:11:26 Q. **Okay. And I think you may have said this, but at the time you wrote this article, were there any FDA-approved treatments for acute attacks of hereditary angioedema?**

14:11:37 A. **Not yet, not at that point.**

14:11:42 Q. **Let me turn back to the demonstratives. I'm going to put up the next slide, PDX-2.3. And can you tell us what is shown on this demonstrative?**

14:11:56 A. **Oh, okay. There we've moved, I guess, to the right, where it says, awards and honors. So there have been a number over the years. They're listed in reverse order, going from '70 to 2013.**

14:12:12 That one is particularly germane, I guess. It
14:12:16 was a research prize for all the work that we had done that
14:12:22 relates to the understanding of what hereditary angioedema
14:12:24 is. It was awarded at an international meeting in Budapest,
14:12:30 and that was in 2013.
14:12:32 Q. And in addition to the awards and honors, what's
14:12:34 listed on the left side of PDX-2.3?
14:12:37 A. Professional organizations with whom I have been
14:12:43 associated. I won't go through the whole thing.
14:12:48 Here is the American Academy of Allergy and
14:12:51 Immunology. That's our national association. I was
14:12:54 president of that in 1989 to 1990. And later up here is the
14:13:00 World Allergy Organization. That's our international
14:13:04 organization. The presidency there is three years, they
14:13:09 make you work, and it was from 2000 to 2003.
14:13:12 And, in fact, there is a joint meeting of those
14:13:15 two organizations in March. That's the one you alluded to
14:13:18 where I'm giving a couple of lectures.
14:13:21 MR. BLUMENFELD: Your Honor, plaintiffs offer
14:13:23 Dr. Kaplan as an expert in the causes and treatment of
14:13:28 hereditary angioedema, including the treatment of acute
14:13:30 attacks of hereditary angioedema.
14:13:34 MR. WIESEN: No objection, Your Honor.
14:13:35 THE COURT: The doctor is accepted as an expert
14:13:37 in that field. Welcome, Doctor.

14:13:39 **THE WITNESS: Thank you.**

14:13:40 **BY MR. BLUMENFELD:**

14:13:40 Q. **Have you prepared a slide, Dr. Kaplan, that summarizes**
14:13:43 **the opinions that you are giving in this case?**

14:13:47 A. **Yes.**

14:13:48 Q. **Let's put up PDX-2.4. And can you tell us what the**
14:13:54 **opinions are that you are giving in this case?**

14:13:56 A. **I guess it's two-fold. That in the year 1989 in**
14:14:02 **particular we had no FDA approved treatments, and what we**
14:14:06 **needed was something that was, of course, safe and effective**
14:14:09 **and reasonably convenient for treatment of acute attacks of**
14:14:13 **HAE.**

14:14:14 **And I assert subsequently that icatibant, the**
14:14:21 **chemical constituent of Firazyr, met the need as being safe,**
14:14:25 **effective, and convenient to treat acute attacks of**
14:14:34 **hereditary angioedema.**

14:14:35 Q. **Thank you.**

14:14:36 **Why don't we find out what hereditary angioedema**
14:14:39 **is. Could you tell us that?**

14:14:40 A. **Yes. It's a genetic disorder, which is why it runs in**
14:14:45 **families. The patients in question will have a mutation in**
14:14:51 **a critical gene. The product of that gene is called C1**
14:14:56 **inhibitor. It's a protein that circulates in plasma. Its**
14:15:01 **function is to inhibit enzymes.**

14:15:04 **When that inhibitor is deficient, meaning**

14:15:08 there's not enough of it, or it's present, but it's not
14:15:11 working, and there's a variety of enzymes then that are not
14:15:16 inhibited normally. The consequence of those enzymes not
14:15:19 being inhibited is the overproduction of bradykinin, the
14:15:24 molecule to which we alluded before. When there is
14:15:26 excessive bradykinin, it leads to the swelling, or
14:15:32 hereditary angioedema.
14:15:33 Q. We'll get back to that in a little while, Dr. Kaplan.
14:15:36 Can you first turn to JTX-18 in your notebook
14:15:40 and tell us what that is?
14:15:41 A. This is another review article, more current. This
14:15:49 was written -- it's titled hereditary angioedema. It's
14:15:54 written by Bruce Zuraw. It's in the New England Journal of
14:16:01 Medicine, September of 2008, and so it is a more recent
14:16:04 review of what the disease is and the various treatment
14:16:09 options.
14:16:11 Q. And does it also describe the symptoms of hereditary
14:16:15 angioedema?
14:16:15 A. It does. It's a good one, and we often use that
14:16:18 clinically when referring to symptoms.
14:16:23 Q. Now, can you tell us a little bit about what the
14:16:28 symptoms of hereditary angioedema are?
14:16:30 A. Sure. The symptoms are -- are of three general types,
14:16:37 and it is helpful to divide them in that way.
14:16:41 One type we call peripheral. So this is

14:16:44 **swelling of hands, feet, face, and genitalia.**

14:16:51 **The second group are visceral. So it's**

14:16:54 **abdominal attacks of swelling. The patient will present**

14:16:58 **with severe abdominal pain akin to a bowel obstruction.**

14:17:04 **It's bad enough to get people into the Emergency Room on a**

14:17:08 **regular basis before we had very specific treatments.**

14:17:14 **Because of the pain, they were often treated with opioids.**

14:17:18 **Many people were addicted to them. Many people were**

14:17:21 **operated on unnecessarily because surgeons who had seen them**

14:17:26 **felt that this was acute and some catastrophe was about to**

14:17:31 **befall them, but yet if they waited it out for three days,**

14:17:34 **it spontaneously regressed. So you have peripheral, you**

14:17:38 **have abdominal.**

14:17:39 **And the third, which is the most feared, is if**

14:17:42 **they have edema of their airway, meaning their larynx, it**

14:17:46 **closes off and they can asphyxiate. So the mortality rate**

14:17:51 **before we had good therapy was close to one in three in that**

14:17:55 **disease.**

14:16:47 Q. **And how many patients, roughly, in the United States**

14:18:17 **are believed to have hereditary angioedema?**

14:18:20 A. **We calculated 16,000, you know, if everybody would**

14:18:27 **die. It is stated in the literature that one in 20,000**

14:18:31 **persons has it and I calculated that from a population of**

14:18:35 **350 million in the U.S. Let's say 16,000 as an upper limit.**

14:18:40 Q. **We are going to turn to some more demonstratives now.**

14:18:46 **Let's go to 2.5, just to help us understand what the**
14:18:53 **symptoms of the disease are. What is shown on 2.5?**
14:18:59 A. **These are two women with a facial attack of hereditary**
14:19:04 **angioedema. For each one, on the left-hand side is the way**
14:19:08 **they normally look. The right-hand side is a severe attack**
14:19:12 **of, attack of hereditary angioedema. It shows the swelling.**
14:19:16 **It tends to be circumferential, even though there is a**
14:19:21 **circle about it, it is quite disfiguring, sometimes the**
14:19:25 **patient is barely recognizable.**
14:19:26 Q. **Is this a frequent symptom of hereditary angioedema?**
14:19:31 A. **In the course of people's lives, this is one of the**
14:19:34 **most frequent. The laryngeal attacks occur in 50 percent of**
14:19:40 **people, the abdominal attacks 90 percent, and this**
14:19:43 **approaches a hundred percent, almost everybody has a hands,**
14:19:47 **foot, feet, facial attack.**
14:19:48 Q. **Approximately how long do the attacks last?**
14:19:51 A. **Three days, we usually say two to four days. Three**
14:19:56 **days is an average.**
14:19:57 Q. **Turning to PDX2.6?**
14:20:04 A. **I will not dwell on it. It is just a hand attack. To**
14:20:07 **give you an idea of what a swollen hand would look like.**
14:20:11 **It's disabling if the person, driving is difficult, if you**
14:20:17 **happen to have a typist, they are done for a few days, and**
14:20:20 **so on.**
14:20:21 Q. **PDX-2.7, can you tell us what is shown here?**

14:20:25 A. **Yes. Mr. Haug actually showed this just briefly in**
14:20:29 **his intro. But this focuses on the larynx. Here is a**
14:20:34 **normal larynx. This is the epiglottis. But here is where**
14:20:38 **the vocal chords would be. I think an arrow points to it.**
14:20:42 **It is not a wonderful slide. It is hard to show.**
14:20:45 **Right here is the opening of the trachea.**
14:20:47 **That's where we breathe. It should be about three-quarters**
14:20:51 **of an inch.**
14:20:52 **If you see on the right, first of all, the**
14:20:54 **anatomy is distorted because this is all swollen. It's like**
14:20:58 **being filled with fluid and what's left of the opening,**
14:21:01 **which here is clearer, is this little space here.**
14:21:05 **The next one I think is better. It doesn't give**
14:21:10 **you a before. But this is right inside of a person's**
14:21:14 **larynx. You will have to know that this is very swollen.**
14:21:20 **But this V is their vocal chord. And here is the opening**
14:21:24 **that this person is trying to breathe through.**
14:21:28 **I would venture, think of it, of trying to**
14:21:31 **inhale through a straw. If this little opening then closes**
14:21:35 **off, it is all over. You can't breathe and you could**
14:21:39 **asphyxiate.**
14:21:40 Q. **That for the record is PDX-2.8.**
14:21:44 **About how many patients with hereditary**
14:21:48 **angioedema experience laryngeal attacks?**
14:21:51 A. **I alluded to it a minute ago. It's about half the**

14:21:55 **patients in the course of the disease will experience**
14:21:59 **laryngeal edema. Of course, it could be frequent. It**
14:22:03 **doesn't have to be one episode. It could be frequent.**
14:22:06 **About 50 percent of the patients are at risk of asphyxiating**
14:22:10 **and the other half tend to get the other kinds of attacks,**
14:22:15 **but often times this one.**
14:22:17 Q. **Is there any cure for hereditary angioedema?**
14:22:20 A. **No, there is no cure. Might be one day we will**
14:22:23 **replace the gene. But we are a long way off.**
14:22:26 Q. **How long has hereditary angioedema been a known**
14:22:31 **disorder?**
14:22:32 A. **1888 seems to be the first mention of it by William**
14:22:35 **Osler. He was at Johns Hopkins. He had many patients with**
14:22:40 **angioedema. But he encountered an unusual group where it**
14:22:44 **segregated in families, like multiple family members would**
14:22:48 **have the same thing. And he noted it was much more severe**
14:22:51 **than the angioedema that he was used to seeing.**
14:22:53 **And he coined the term, he called it a little**
14:22:56 **differently at the time, it was, I think you might have a**
14:23:01 **page on that, it was hereditary angioneurotic edema. He**
14:23:07 **found -- he coined the term because the patient seemed so**
14:23:13 **fearful and anxious that he thought it was a kind of**
14:23:16 **neurosis that led to swelling long before We knew it had**
14:23:21 **anything to do with blood proteins.**
14:23:22 Q. **Do you have the Osler article?**

14:23:27 A. **It is one of these tabs.**

14:23:28 Q. **Can you look at PTX-180?**

14:23:32 A. **Yes. That is the original article. If you look down, it's interesting, the little footnotes, No. 5 caught my eye, because it's abstract in the London recorded December 1887. I guess in abstract form he had made a presentation about his discovery and then it came out the next year in an article.**

14:23:58 Q. **Dr. Kaplan, what causes the swelling that is associated with an acute attack?**

14:24:04 A. **The molecule that causes the swelling is bradykinin. We have been hearing about it all day, as well as antagonists. I think we have a simplified diagram that could show that. There it is.**

14:24:21 **What is shown here? So here is bradykinin. It's a nine-amino-acid peptide, as you have heard on numerous occasions. It is produced from a protein that circulates called kininogen, the HMW stands for high molecular weight, meaning it's big. Kininogen is cleaved by an enzyme, not shown here, and it produces bradykinin.**

14:24:46 **Bradykinin binds to a receptor that is on the surface of endothelial cells. It is important to note that endothelial cells line your blood vessels. So when bradykinin interacts with the receptor, it activates the cells. When the cells are activated, they separate, which**

14:25:05 **is they dilate. And if you could see, it would look red.**

14:25:09 **When the cells separate, there are spaces made**

14:25:13 **in between the cells. So fluid leaks out, which is listed**

14:25:18 **here as increased vascular permeability. So fluid leaks out**

14:25:22 **from the vessels into the surrounding issue. That is what**

14:25:26 **angioedema is.**

14:25:27 **That is what you see in the hand. It had leaked**

14:25:32 **from the hand vessels into the subcutaneous tissue right**

14:25:36 **under the skin and all puffed out as angioedema.**

14:25:39 Q. **I want to take us back -- forward from 1887. What**

14:25:45 **were the options for treating an acute attack back in 1989?**

14:25:50 A. **In '89, we did not have what you would consider a**

14:25:54 **specific treatment. So you tried, number one, to make the**

14:26:00 **patient comfortable. You needed observation to try to**

14:26:05 **prevent the more serious manifestations.**

14:26:09 **Example, a person with an abdominal attack shows**

14:26:12 **up in the emergency room. They will get an intravenous so**

14:26:15 **they will get fluid because sometimes patients dehydrate.**

14:26:19 **They can get pain medication, opiates if necessary. And**

14:26:22 **they could be observed further.**

14:26:25 **The laryngeal edema, a patient comes into the**

14:26:29 **emergency room, and they will set up for what is needed for**

14:26:33 **at least the possibility they might have to do a**

14:26:36 **tracheostomy into the airway if the person was at risk of**

14:26:39 **asphyxiation.**

14:26:40 So there was nothing they could do to stop it, but they could save the patient from dying before their eyes.

14:26:45 Q. Let me put up demonstrative 2.10. Could you tell us what is shown here?

14:26:53 A. This is one patient, No. 1 is meant to show you how the person looks normally. I don't know the time difference. Let's just say in No. 2 the person woke up that morning and he obviously has facial swelling. It gets progressively worse, so he goes to the emergency room where he is being observed. While he is being observed he starts to have difficulty breathing. And they put in a nasotracheal tube.

14:27:19 So this is a tube that went up his nose and then around your throat and back down into the larynx, into the airway that I showed you earlier.

14:27:29 If it were too narrow to do that and you couldn't do it, you would have to do a tracheostomy, which is a surgical procedure to literally put a hole in his neck and put a tube in.

14:27:40 Q. Was fresh frozen plasma also used sometimes?

14:27:46 A. Yes. Back at that point, and I was, of course, active in seeing patients at that time, fresh frozen plasma was the only thing we had that we could actually give the patient. I had used it in some. But it really is a dangerous,

14:28:02 potentially dangerous approach to it. It is no longer used.
14:28:08 Q. Can you explain why?
14:28:13 A. This rather complex slide is a teaching slide that I
14:28:16 use. But I am only going to talk about the right-hand side.
14:28:21 It kind of repeats what you saw previously.
14:28:24 Here is the bradykinin. Here is the kininogen from which it
14:28:28 is derived. And I added the enzyme that makes it. So
14:28:31 kallikrein is the enzyme that makes bradykinin by cleaving
14:28:36 kininogen. This little vertical box, as we see, one
14:28:39 inhibitor normally works, so the idea of fresh frozen
14:28:42 plasma, because it's normal plasma, is, the patient is
14:28:45 deficient in this protein so let's give it back. So you
14:28:48 infuse the person with the fresh frozen plasma, their C1
14:28:53 inhibitor level rises. And if it inhibits this enzyme, they
14:28:57 ought to get better.
14:28:59 The problem is with plasma, you are also giving
14:29:02 them this protein, kininogen. And when they are having an
14:29:06 attack, there is lots of kallikrein in the patient's
14:29:09 circulation. And kallikrein cleaves kininogen rapidly,
14:29:13 sometimes more rapidly than the inhibitor can kill the
14:29:16 kallikrein. And therefore the bradykinin levels rise before
14:29:20 the patient gets better.
14:29:22 So that's dangerous because the patient could
get worse.
14:29:26 If I were doing it now and had nothing available

14:29:29 to me, I would never use it in a laryngeal attack. I would
14:29:33 think about it in on abdominal attack. But I could in the
14:29:36 proper setting perhaps in a peripheral attack to shorten the
14:29:41 course.
14:29:41 Q. Since 1989 has the FDA-approved any treatments for
14:29:49 hereditary angioedema?
14:29:51 A. Sure. Now we have multiple treatments.
14:29:53 Q. Are two of those drugs called Berinert and Kalbitor?
14:29:59 A. For sure.
14:29:59 Q. Can you take a look at JTX-21 in your book and tell us
14:30:05 what that is?
14:30:07 A. 21, okay, that is Berinert. This is the package
14:30:14 insert. It tells you the indications, usage, dosage, side
14:30:18 effects and so forth.
14:30:19 Q. What year is that from?
14:30:21 A. This is from 2009, which is the year in which it was
14:30:24 approved.
14:30:25 Q. And what was or is the active ingredient in Berinert?
14:30:32 A. Berinert is a preparation of C1 inhibitor, which I
14:30:35 alluded to with regards to the fresh frozen plasma. But it
14:30:39 is purified. So it doesn't have any of the other proteins.
14:30:42 So it cannot do what I described before, where the patient
14:30:47 would get worse before they got better.
14:30:49 Q. In 2009, what were the indications for which Berinert
14:30:56 was approved?

14:30:56 A. **At this point in time, you can read here, under**
14:30:59 **Indications, I guess you have it in yellow, it says**
14:31:03 **"Treatment of acute abdominal attacks or facial attacks" --**
14:31:08 **I think they meant peripheral -- or hereditary angioedema in**
14:31:13 **adults and adolescent patients. At that point in time,**
14:31:15 **laryngeal attacks were not included.**
14:31:17 Q. **Was it later approved for laryngeal attacks?**
14:31:20 A. **It was, about two years later. Two years and some**
14:31:23 **months.**
14:31:23 Q. **And how is Berinert administered?**
14:31:32 A. **Berinert is administered intravenously. In 2009,**
14:31:40 **first of all, it was the first one at that point, and so if**
14:31:44 **you had an attack of angioedema, you went to your healthcare**
14:31:49 **provider, which usually meant the doctor's office or to the**
14:31:51 **emergency room, they would have the setup, and you would**
14:31:54 **receive it intravenously to treat the acute attack.**
14:31:59 Q. **Later, was it approved for self-administration?**
14:32:02 A. **Yes. At the time, maybe December of 2011, at the same**
14:32:11 **time that the laryngeal attacks were added to their**
14:32:15 **approval, it was then approved for self-administration. We**
14:32:19 **can get back to that perhaps a little bit later.**
14:32:22 **But before that other things had happened.**
14:32:24 Q. **Now, are there problems with intravenous**
14:32:32 **administration of a drug for acute attacks?**
14:32:37 A. **Well, our -- if you have nothing, there is no problem.**

That is how we started out.

But a variety of medications can be given subcutaneously. Like insulin, a simple injection under the skin. So that's simpler. Faster. More convenient. And you are then not driving to another site to have administration.

If you are at the stage where you can self-administer it, it is the difference between trying to make up the material, your own IV, versus taking something that might be preformed, by preformed I mean already drawn up in a syringe, and simply quickly inject yourself.

So you can't compare a quickie subcutaneous injection with going through the whole rigamarole of preparing the material and starting your own intravenous.

Q. **Could you turn to JTX-47, and tell us what that is?**

A. **47 is the package, the comparable package insert for Kalbitor, the chemical name for that is ecallantide.**

Q. **Was that also approved in 2009?**

A. **The same year, ending a few months apart. That was approved for acute attacks of hereditary angioedema.**

Q. **Right in the middle, the first column, there is a box, it says warnings: Anaphylaxis. Can you tell us what that is?**

A. **Yes. When Kalbitor came out there was also a lot of excitement, for two reasons. First, the Kalbitor was the**

14:34:30 first one that was subcutaneous. So we could draw it up in
14:34:34 a syringe and inject it immediately and got around the whole
14:34:37 business about intravenous administration.
14:34:41 But it had a big "but," it turned out, in all
14:34:44 the studies, that Kalbitor had in certain instances of
14:34:47 causing of allergic reactions. It was about three percent.
14:34:50 Some of those allergic reactions were anaphylactic, which is
14:34:53 what we use EpiPens for, the most severe allergic reactions.
14:34:57 So it did get approved but it was with a but.
14:35:00 That was with a black box warning that even though it could
14:35:05 be drawn up in the syringe and given quickly subcutaneous,
14:35:08 the patient, if they said no to self-administration, the
14:35:12 patient had to have a healthcare provider actually give them
14:35:17 the medication so they could either go to their doctor or
14:35:20 the emergency room, or, I know Dyax, who was the
14:35:24 manufacturer at the time, worked out a mechanism by which
14:35:28 you could make a telephone call and a health care person
14:35:30 actually came to the home of the patient and administered
14:35:33 the drug.
14:35:35 So a double-edged sword, if you will. The
14:35:39 ability to administer it quickly because it's right in the
14:35:42 syringe, you don't have to make much stuff or start an IV,
14:35:46 but you couldn't do it yourself and you would now have the
14:35:49 time interval in getting help in order to get your medicine.
14:35:53 Q. After these two drugs were available in 2009, was

14:35:57 there still a need for other treatments for acute attacks?
14:36:01 A. Yes. My feeling is, because you would like to combine
14:36:05 all of the positive things that happened in one drug, so the
14:36:10 subcu here is terrific. But you have got a big negative
14:36:14 with allergic reactions.
14:36:18 Berinert was effective, it was reasonably safe.
14:36:22 But starting IVs is a much more difficult thing than a
14:36:27 simple subcutaneous medicine that you could administer
14:36:32 yourself, because it could be preloaded. If you think you
14:36:35 are having an attack, you could get it in in five seconds.
14:36:38 That happened, that's where you are alluding to, where
14:36:42 icatibant first came out, which was two years later.
14:36:45 Q. Icatibant is the --
14:36:47 A. Firazyr, if you will.
14:36:48 Q. Could you turn to JTX-45 in your book. What is
14:36:56 JTX-45?
14:36:57 A. So this is the package insert for Firazyr,
14:37:02 (icatibant), approval 2011.
14:37:05 Q. What indications was Firazyr approved for?
14:37:10 A. For acute attacks of hereditary angioedema in adults
14:37:13 18 years or older. So it was at that time restricted to
14:37:18 adults. Acute attacks here meant everything, Peripheral,
14:37:24 gastrointestinal, or laryngeal.
14:37:25 Q. How is it administered?
14:37:27 A. A single injection. It was in -- it was in a

14:37:33 **preloaded syringe. That's how it comes. So it's ready to**
14:37:36 **go.**
14:37:36 Q. **For subcutaneous --**
14:37:39 A. **For subcutaneous administration. And approved for**
14:37:46 **self-administration. It was the first one I believe that**
14:37:49 **was approved for self-administration.**
14:37:50 Q. **Have you ever prescribed Firazyr?**
14:37:53 A. **I have not. When I alluded to earlier, when I retired**
14:37:57 **from clinical practice, these drugs were first coming on.**
14:38:02 Q. **Now, is icatibant or Firazyr a bradykinin B2 receptor**
14:38:10 **antagonist?**
14:38:10 A. **Yes.**
14:38:11 Q. **And I am going to put up another slide, which is**
14:38:21 **PDX2.12. Can you explain to us what that means?**
14:38:26 A. **I will be brief.**
14:38:28 **You saw the slide a minute ago. The only thing**
14:38:30 **added is to point out that icatibant is a B2 receptor**
14:38:36 **antagonist, where the X is then the site at which it works.**
14:38:41 **It's going to block the ability of bradykinin to**
14:38:46 **interact with its receptor. Since a patient who is having**
14:38:49 **an attack has a very high concentration in their blood of**
14:38:53 **bradykinin, as soon as the drug gets in, it will block that.**
14:38:57 **That's how it stops an attack.**
14:38:23 Q. **And is that the same way that Berinert or Kalbitor**
14:38:46 **work?**

14:38:46 A. **They have a different mechanism. They work**
14:38:50 **actually -- well --**
14:38:52 Q. **Let me put up the next slide.**
14:38:53 A. **Yes. Prior to that. This is as far as we got in the**
14:38:59 **cascade. You've seen Kallikrein before. That's the enzyme.**
14:39:08 **Where a C1 inhibitor or Berinert works is in the little blue**
14:39:13 **dot and Kalbitor is in the little green dot. Kallikrein, so**
14:39:19 **we look here, first at the down line. Ecallantide inhibits,**
14:39:26 **right there and C1 inhibitor also does.**
14:39:35 **So one effect is to block this enzyme and**
14:39:38 **therefore, once that gets in, the person will not produce**
14:39:41 **more bradykinin. They differ from icatibant in that they**
14:39:46 **don't do anything immediately about the bradykinin that's**
14:39:49 **already there.**
14:39:50 **Icatibant, by contrast, doesn't do anything**
14:39:53 **about producing bradykinin. It simply stops the molecule**
14:39:58 **right then and there, which relates to acute kinds of**
14:40:02 **therapy. A C1 inhibitor has more stops in this cascade than**
14:40:14 **-- Icatibant is where there's an X. There are two enzymes**
14:40:18 **in this process. Factor 12 means it's active. That's an**
14:40:22 **enzyme and Kallikrein is an enzyme. C1 inhibitor inhibits**
14:40:27 **both enzymes and Kalbitor inhibits the second one.**
14:40:29 Q. **Thank you, Dr. Kaplan.**
14:40:30 **I'm going to turn to the next demonstrative,**
14:40:33 **2.14. And is this a demonstrative you prepared on the**

14:40:36 **attributes of Firazyr?**

14:40:38 A. **Yes. Tried to summarize. It's safe. It's effective.**
14:40:41 **It is only marketed for acute attacks. There is such a**
14:40:45 **thing as prophylaxis. None of these drugs that we're**
14:40:48 **talking about today, at least not in that context. Acute**
14:40:52 **attacks.**

14:40:53 **They have no allergic reactions, and no**
14:40:58 **anaphylaxis. It has no systemic side effects. The only**
14:41:02 **side effects I'm aware of are due to the local injection.**
14:41:07 **Some people feel a little burning when you inject it, and it**
14:41:10 **usually looks red after you remove the needle, but that's**
14:41:13 **it. And I don't think there's anybody who doesn't use the**
14:41:16 **drug because of the local side effect.**

14:41:18 **It comes in a good, a dosage form, if you will,**
14:41:22 **because it's the only one that you don't even have to draw**
14:41:25 **the stuff up. It's in a preloaded syringe. It's also quite**
14:41:30 **stable. It's good between two degrees and 25 degrees, and**
14:41:33 **25 is basically room temperature. So you can just have it**
14:41:37 **out in a place that's convenient for you. It's stable and**
14:41:40 **it doesn't go bad for long periods of time. Refrigeration**
14:41:47 **is not required.**

14:41:48 **So finally, if you are having an attack and are**
14:41:51 **sitting right there, you can administer as a single**
14:41:54 **subcutaneous injection.**

14:41:56 **For laryngeal attacks in particular, all**

14:41:59 guidelines say no matter what therapy you're using, get the
14:42:02 therapy, assuming it's self administered, get in your car
14:42:06 and go to an Emergency Room.
14:42:07 This one has an advantage that you could have a
14:42:09 second one sitting in the glove compartment of your car and
14:42:12 if you get scared or it seems like it's not going well, you
14:42:15 could shoot yourself a second time on the way.
14:42:18 Q. In your opinion, Dr. Kaplan, are all of these
14:42:23 attributes related to the active ingredient icatibant?
14:42:29 A. Yes. The effectiveness, of course, is due to the
14:42:34 drug. It didn't have to be safe, but it is, as are other
14:42:39 ones. The fact that it's soluble and stable allows it to be
14:42:44 doled out, if you will, in this fashion.
14:42:47 It's the smallest of all the molecules we have.
14:42:52 Molecular weight is about 1300, a little bigger than
14:42:56 bradykinin itself, and small molecules diffuse very fast
14:43:02 through the skin into the bloodstream. I don't want to
14:43:06 misstate that. Not every one will do that, but in general,
14:43:11 little ones do it and it gets through quickly, and because
14:43:15 of that, intravenous administration was not needed because
14:43:20 it would diffuse rapidly and you get a sufficient blood
14:43:22 level to block the bradykinin that is there.
14:43:24 Q. Have you prepared a chart comparing some of the things
14:43:30 that are the same and things that are different between
14:43:33 Firazyr, Berinert and Kalbitor?

14:43:36 A. **I think we have what you would consider a summary of**
14:43:41 **the main ones.**
14:43:44 Q. **Could you take a look at that and explain?**
14:43:47 A. **C1 inhibitor, Berinert. Ecallantide, Kalbitor,**
14:43:57 **Icatibant, Firazyr. Bradykinin B2 receptor. That's the way**
14:44:02 **Firazyr happens to work.**
14:44:03 **Berinert in 2011 as it was -- up to -- we put**
14:44:11 **2011 here. Berinert was approved for abdominal and facial**
14:44:17 **and even at this, in 2009, even at this point, the laryngeal**
14:44:21 **had not yet gotten there. It took about two, three months**
14:44:24 **there and then laryngeal was included.**
14:44:27 **Kalbitor came out about the same time and it was**
14:44:31 **approved for all HAE attacks.**
14:44:33 **Firazyr came out in '11 and all HAE attacks were**
14:44:38 **included in its original approval. Both Berinert and**
14:44:44 **Kalbitor when they appeared required a healthcare worker.**
14:44:50 **Either you called them, or in this instance simply went to**
14:44:53 **your doctor or your Emergency Room. Firazyr was immediately**
14:44:56 **okay for self-administration.**
14:44:58 **To this day, Kalbitor cannot be**
14:45:02 **self-administered because of the black box. Berinert can.**
14:45:06 **A few months after Firazyr got theirs, that's when they,**
14:45:11 **too, were okay for self-administration.**
14:45:13 **Berinert is IV no matter who gives it. Kalbitor**
14:45:18 **is subcutaneous. Firazyr is subcutaneous, and it is the**

14:45:23 only one that's preloaded in the syringe. It's simply the
14:45:27 fastest. And the black box warning, of course, is unique to
14:45:31 the Kalbitor because of the allergic reaction.
14:45:33 Q. Thank you, Dr. Kaplan. Just a couple more questions.
14:45:36 Is it from a clinical point of view important
14:45:41 that Firazyr is indicated for self-administered subcutaneous
14:45:48 injection?
14:45:49 A. Yes. What we all knew and had talked about a lot over
14:45:58 these ensuing years. At first it was just a perception, no
14:46:04 proof. That seems the faster you got the medicine into the
14:46:08 patient who appeared, the faster they responded to it and
14:46:10 were less likely to get one of the severe manifestations.
14:46:14 That was formally studied by Marcus Maurer. I was included
14:46:19 in the group as well. That was a subsequent publication. I
14:46:23 think it's in our group.
14:46:25 Q. Would you look at PTX-227?
14:46:33 A. 27?
14:46:34 Q. Is this the Maurer article you were talking about?
14:46:38 A. Yes. I have it. This is the article that I'm
14:46:40 speaking of. So this was -- it was published in 2013. It's
14:46:48 one of the only articles we have to try to take this
14:46:51 perception and say, well, is it real if you study it?
14:46:54 Icatibant was the drug that was chosen to do the
14:46:57 study, and in short what it showed was the faster you got
14:47:02 the drug into the patient, the better was the outcome.

14:47:05 Q. **Was that --**

14:47:06 A. **They responded more quickly, less likely to have a**
14:47:10 **progression to the more severe manifestations.**

14:47:12 Q. **And is that shown in the conclusions?**

14:47:16 A. **Yes. The conclusion, I'm reading it here. From here,**
14:47:19 **it's early blockade of the bradykinin B2, receptor with**
14:47:25 **icatibant, particularly within the first hour of an attack**
14:47:30 **onset, significantly reduced attack duration and time to**
14:47:33 **attack resolution.**

14:47:36 **So that's one of the advantages of**
14:47:37 **icatibant in the sense that it -- you don't have to dissolve**
14:47:40 **it up. It's ready to go in the syringe. It's approved for**
14:47:43 **self-administration, so the person can get it in as soon as**
14:47:46 **they're aware of the fact that an attack has occurred,**
14:47:51 **that's as fast as you can go, and that gives you a better**
14:47:55 **outcome.**

14:47:57 **And as I said, after the laryngeal, it's not**
14:48:00 **covered by this, but laryngeal is really dangerous, and**
14:48:04 **we're not cavalier by assuming one shot fixes everybody. So**
14:48:10 **if you get up into your car real and leave, first of all,**
14:48:13 **you can do it real fast and get out. And, secondly, you**
14:48:14 **could self-administer a second one while you're driving if**
14:48:17 **you have to.**

14:48:17 **MR. BLUMENFELD: Thank you, Dr. Kaplan. Your**
14:48:19 **Honor, I don't have any further questions.**

14:48:21 **THE COURT: All right, Mr. Blumenfeld.**

14:48:24 **Mr. Wiesen, your cross?**

14:48:26 **MR. WIESEN: Thank you. We'll distribute some binders quickly, if we can.**

14:48:28

14:48:30 **THE COURT: All right.**

14:48:30 **(Binders handed to the Court and to the witness.)**

14:48:50

14:48:51 **MR. WIESEN: Your Honor, we're going to distribute two binders, one with some exhibits and one with a report and deposition, although I'm expecting we won't need the report and deposition, but we'll distribute it.**

14:48:53

14:48:55

14:48:58

14:49:02

14:49:02 **THE COURT: All right.**

14:49:37 **CROSS-EXAMINATION**

14:49:38 **BY MR. WIESEN:**

14:49:38 Q. **Good afternoon, Dr. Kaplan.**

14:49:41 A. **Hi, Mr. Wiesen.**

14:49:42 Q. **How are you?**

14:49:42 A. **Good. And you?**

14:49:44 Q. **Good. I actually want to start in your exhibit binder and look at that article you were just talking about.**

14:49:47

14:49:50 A. **Last one?**

14:49:58 Q. **PTX-227. Now, this paper only studies icatibant; is that correct?**

14:50:08

14:50:08 A. **Correct.**

14:50:09 Q. **Not a head-to-head study between icatibant and**
14:50:12 **Berinert, is it?**
14:50:14 A. **Agreed. It is not.**
14:50:15 Q. **Not a head-to-head study between icatibant and**
14:50:19 **Kalbitor?**
14:50:20 A. **Correct.**
14:50:21 Q. **And if we pull up that conclusion that you had in the**
14:50:24 **abstract, the definition you used in this study for a quick**
14:50:33 **response with getting the drug on board the patient within**
14:50:37 **an hour; is that correct?**
14:50:38 A. **Correct.**
14:50:39 Q. **And certainly patients can get Berinert even by IV on**
14:50:44 **board within an hour at home; is that correct?**
14:50:46 A. **Correct.**
14:50:47 Q. **And certainly patients can get Kalbitor on board**
14:50:52 **within an hour; is that right?**
14:50:53 A. **Possible, sure.**
14:50:54 Q. **So the logic of this paper doesn't really distinguish**
14:50:57 **between icatibant and Kalbitor and Berinert. It just says,**
14:51:02 **go quickly, which makes sense?**
14:51:04 A. **Right.**
14:51:04 Q. **You didn't mean to suggest that this paper is an**
14:51:07 **advantage for icatibant compared to Berinert and --**
14:51:11 A. **No.**
14:51:12 Q. **-- Kalbitor. Right?**

14:51:14 A. **I did not in -- let me make what the point is, because**
14:51:18 **you know there are no head-to-head direct studies. It makes**
14:51:25 **a generic point, and I would make that point for the other**
14:51:27 **drugs as well. The faster you get it in, the better outcome**
14:51:32 **you're likely to have. And it only relates to when you**
14:51:37 **think about the various drugs, how fast can you get it in.**
14:51:41 **And, yes, I would agree with you, all of them usually can be**
14:51:45 **gotten in within an hour, but maybe some could get in in**
14:51:48 **five minutes and other ones take 35 minutes.**
14:51:51 Q. **Well, if we turn to 227.4, we'll put it up, Table 4 at**
14:51:56 **the bottom in this paper.**
14:52:00 **If we look at the left-hand side, the categories**
14:52:03 **of timing used are less than an hour or greater than an**
14:52:06 **hour; is that right?**
14:52:07 A. **Yes. Are we on the same --**
14:52:10 Q. **Same document.**
14:52:11 A. **Yes. Table 4. I've got it.**
14:52:14 Q. **We've got it up on the screen if you want or you can**
14:52:16 **look in the binder.**
14:52:17 A. **Yes.**
14:52:18 Q. **The category of time you used greater than an hour or**
14:52:22 **less than an hour?**
14:52:23 A. **Yes.**
14:52:23 Q. **Greater than two or less than two. Right?**
14:52:26 A. **Yes.**

14:52:26 Q. **And greater than five or less than five. Correct?**
14:52:29 A. **Correct.**
14:52:30 Q. **So there's no analysis in this paper even for icatibant of whether there's a difference between five minutes and fifteen minutes; is that right?**
14:52:36 A. **Correct.**
14:52:37 Q. **No one studied that; right?**
14:52:38 A. **Correct.**
14:52:40 Q. **All right. You can put that one aside then.**
14:52:40 **Now, Dr. Kaplan, I think you told Mr. Blumenfeld that you've never prescribed Kalbitor; is that right?**
14:52:44 A. **I did.**
14:52:50 Q. **Is that because -- let me back up. You've never prescribed icatibant?**
14:52:53 A. **That's correct.**
14:52:54 Q. **That's because it was approved after you stopped treating patients?**
14:52:57 A. **Sure.**
14:52:59 Q. **That's approved in the United States?**
14:52:59 A. **Correct.**
14:53:02 Q. **Because that's what you were talking about in your testimony, FDA approval in the United States; is that correct?**
14:53:03 A. **Correct.**
14:53:03 Q. **You weren't talking about how these drugs are**
14:53:04
14:53:05
14:53:07
14:53:09
14:53:09
14:53:10

14:53:12 **approved or used in Europe; is that right? And you weren't**
14:53:15 **talking about how these drugs might be used even if it's**
14:53:19 **off label or beyond what the label specifically said; is**
14:53:21 **that correct?**
14:53:21 A. **Correct.**
14:53:22 Q. **Your testimony on direct was just very specifically**
14:53:26 **about what the FDA label says in the United States; is that**
14:53:29 **right?**
14:53:29 A. **True.**
14:53:30 Q. **And you stopped treating patients before Berinert was**
14:53:34 **approved in the United States; is that correct?**
14:53:35 A. **Sure. Yes. Well, just about. Yes. That one is**
14:53:39 **close, but the answer is yes.**
14:53:41 Q. **And so you've never prescribed Berinert?**
14:53:43 A. **No.**
14:53:43 Q. **And you've never prescribed Kalbitor?**
14:53:45 A. **No.**
14:53:46 Q. **So you've never had to sit down with a patient and try**
14:53:48 **and decide which of these particular drugs to administer to**
14:53:52 **that patient; is that correct?**
14:53:53 A. **That's correct.**
14:53:54 Q. **Now, I think it's fair to say you're a world renowned**
14:53:58 **expert in HAE; is that correct?**
14:54:00 A. **I think so.**
14:54:01 Q. **And you've been treating patients with HAE for**

14:54:04 **30 years?**

14:54:05 A. **Forty.**

14:54:05 Q. **Forty years. And in all of that time, you've only**
14:54:10 **seen about six to eight patients who are actually suffering**
14:54:14 **from an acute attack; is that correct?**

14:54:15 A. **Correct. Most of the patients that I've seen were**
14:54:21 **diagnostic dilemmas, so on and so forth, but to walk in the**
14:54:26 **office at that time, I would say half a dozen is about**
14:54:30 **right.**

14:54:30 Q. **Of that half dozen, you've only treated half of that**
14:54:33 **half dozen, right, because half of them, the swelling was**
14:54:37 **not significant enough to need any treatment at least based**
14:54:39 **on what was available at the time?**

14:54:40 A. **Yes. But what we meant when I said some was around**
14:54:45 **four or six, but I meant that number I actually treated was**
14:54:48 **something. Usually, it was the fresh frozen plasma.**

14:54:53 Q. **So in the 40 years you've been treating HAE patients,**
14:54:56 **it's four to six acute attacks that you've treated over the**
14:55:00 **years?**

14:55:01 A. **Correct.**

14:55:01 Q. **Now, part of the reason it's so few, there are not a**
14:55:09 **lot of patients in the United States with HAE; is that**
14:55:12 **correct?**

14:55:12 A. **Correct.**

14:55:13 Q. **And certainly not a lot of patients who are diagnosed**

14:55:15 with HAE?
14:55:17 A. Also correct.
14:55:17 Q. You estimated about 16,000. That's because based on a
14:55:21 prevalence of one in 20,000; right?
14:55:23 A. Right.
14:55:23 Q. But there's only maybe 3 or 5,000 patients in the
14:55:26 United States who are actually treated, diagnosed and
14:55:29 treated for HAE; is that correct?
14:55:32 A. The figure I had was eight, but let's not quibble.
14:55:36 Q. Less than 10,000?
14:55:38 A. Less than 10,000.
14:55:39 Q. And so the target market for a drug like icatibant is
14:55:43 less than 10,000 people in the United States?
14:55:45 A. Yes.
14:55:46 Q. And that's true for Berinert and Kalbitor as well?
14:55:53 A. As long as they've got that disease, their potential
14:55:56 would be maybe 16,000 if every single person was diagnosed,
14:56:02 which we know is not the case.
14:56:03 Q. We know that's part of the problem. It takes a long
14:56:06 time to diagnose patients?
14:56:07 A. Yes.
14:56:07 Q. Ten or 20 years some of the literature suggests?
14:56:10 A. That's an old one, but the latest study, and that's
14:56:17 now passe, too, but it was about eight years, it's a Mike
14:56:23 Frank paper, about eight years before people at that point

were diagnosed. I suspect we're doing a lot better now only because, first of all, it was about the time that these drugs were coming on.

And, secondly, there's a tremendous amount of education regarding it, so I think we're doing much better in diagnosing it, but that hasn't been a subsequent paper that would give you the most current figure.

Q. But the figure you have was 8,000 diagnosed patients at the outside?

A. Right.

Q. In the United States.

Now, icatibant is not the only treatment for HAE that Shire manufactures and sells; right?

A. You know, Shire has icatibant.

Q. Right.

A. They acquired Firazyr -- they acquired Kalbitor from Dyax.

Q. Right?

A. And they have Cinryze.

Q. Correct. And Cinryze is one of these prophylactic treatments; is that right?

A. It is.

Q. It's actually basically the same drug as Berinert, isn't it?

A. Yes.

14:57:28 Q. **But it's approved in the United States. It's the C1**
14:57:31 **INH inhibitor that's approved for prophylaxis?**
14:57:37 A. **For prophylaxis.**
14:57:38 Q. **And Berinert is basically the same drug, but approved**
14:57:42 **because of different clinical trials for acute attacks;**
14:57:44 **correct?**
14:57:45 A. **May I make a point that you remind me of?**
14:57:51 **Prophylaxis, forgetting androgens from past years,**
14:57:56 **prophylaxis, you either do it intravenously or you don't do**
14:57:59 **it. In the U.S., Cinryze is the one that is approved.**
14:58:03 **That's a twice-a-week intravenous injection.**
14:58:08 **So the person who is on prophylaxis, and we**
14:58:11 **have lots of folks, a large percentage of that small number**
14:58:14 **of people receiving intravenous. One of the problems is**
14:58:19 **that's a twice-a-week intravenous injection getting IV**
14:58:24 **stuff.**
14:58:25 **Now, everybody breaks through occasionally**
14:58:27 **and gets an attack. Would you wish to treat the attack with**
14:58:33 **yet another intravenous medication, because as time goes on,**
14:58:38 **even people with good veins become tougher and tougher to**
14:58:44 **get the needle into their vein. And there are some, as you**
14:58:46 **know, who it's not fun getting a needle in their stomach.**
14:58:52 **So the availability of a quick subcutaneous**
14:58:58 **injection that's convenient is really a big deal for the**
14:59:02 **people who are on the prophylaxis, because they're getting**

14:59:05 **IVs all the time.**

14:58:52 Q. **Dr. Kaplan, I think it will go a little more quickly**
14:59:27 **if you just respond to the questions. If Mr. Haug has some**
14:59:30 **followup about those issues, he can get into that.**

14:59:33 A. **Okay.**

14:59:33 Q. **Now, you agree that icatibant was not the first safe**
14:59:40 **effective easily administered drug for acute attacks**
14:59:43 **approved in the United States. Right?**

14:59:46 A. **Well, when Berinert came in, we were very excited**
14:59:51 **about it. It was fast. It was safe, it was effective. I**
14:59:55 **know in my deposition you asked me that very question.**

14:59:57 Q. **And you agreed with it. Right?**

14:59:59 A. **And I agreed with it. But you know, it's different.**
15:00:02 **You didn't ask me the question compared to anything else.**

15:00:06 **Also, think about this.**

15:00:08 **In 2009, when it was first approved --**

15:00:11 Q. **Dr. Kaplan, if you could just let me ask a question?**

15:00:15 A. **When it was first approved, you had to go to the**
15:00:19 **physician to do it. My translation of that question is a**
15:00:23 **patient comes into me, do I think it's easy to put the IV in**
15:00:27 **them and give them the drug? My answer was yes.**

15:00:29 Q. **You would agree that the approval of Berinert in the**
15:00:32 **United States was an enormous milestone in the treatment of**
15:00:35 **HAE. Correct?**

15:00:36 A. **I agree.**

15:00:37 Q. **And it was an enormous milestone in 2009. Correct?**

15:00:52 A. **That's when it was. Yes.**

15:00:54 Q. **Now, if you look at JTX-21 in the cross-examination binder.**

15:01:08

15:01:36 A. **Oh, my Heaven's, I have a different one. The Berinert insert?**

15:01:52

15:01:53 Q. **Correct. If we look at this at the top, this was approved in October of 2009. Correct?**

15:02:03

15:02:06 A. **Correct.**

15:02:06 Q. **And the indications were Berinert is for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients. Right?**

15:02:15

15:02:19

15:02:20 A. **Correct.**

15:02:21 Q. **And this is before icatibant's approved. Right?**

15:02:25 A. **Yes.**

15:02:25 Q. **Now, this approval in the United States for Berinert was in October of 2009. Right?**

15:02:29

15:02:32 A. **Yes.**

15:02:32 Q. **Would you agree that Berinert had been used in Europe for years before that? Right?**

15:02:36

15:02:37 A. **Yes.**

15:02:37 Q. **It had been used starting in the late seventies at least. Correct?**

15:02:41

15:02:42 A. **Correct.**

15:02:42 Q. **Now, I think you pointed out that this initial**

15:02:47 **approval in the United States did not explicitly include**
15:02:51 **laryngeal attacks in the indications. Right?**
15:02:54 A. **That's correct.**
15:02:55 Q. **But for years you know that Berinert had in fact been**
15:02:58 **used for laryngeal attacks in Europe well before 2009.**
15:03:02 **Right?**
15:03:02 A. **Right.**
15:03:03 Q. **And you knew that because your European colleagues,**
15:03:05 **like the World Allergy Organization, told you about that.**
15:03:09 **Correct?**
15:03:10 A. **Correct.**
15:03:10 Q. **And if we turn to Page 14 of JTX-21, this is the U.S.**
15:03:18 **label in 2009, we know there is actually some reference to**
15:03:24 **laryngeal attacks. Right?**
15:03:26 A. **Could you just give me the page number.**
15:03:28 Q. **JTX-21.14, the very bottom paragraph?**
15:03:36 A. **In the rare case, I see.**
15:03:37 Q. **It specifically says, "In the rare case that a subject**
15:03:41 **developed life-threatening laryngeal edema after inclusion**
15:03:44 **into one of the clinical studies, immediate start of open**
15:03:48 **label treatment with a 20 unit per kilogram body weight dose**
15:03:52 **of Berinert was allowed."**
15:03:54 **Right?**
15:03:55 A. **Right.**
15:03:55 Q. **So even though laryngeal attacks weren't specifically**

15:03:58 **approved, they were referenced on the label for Berinert in**
15:04:02 **the United States starting in 2009?**
15:04:04 A. **I think that -- well, it says -- in the course of**
15:04:08 **events as the study was going on, if somebody had one, you**
15:04:11 **did it.**
15:04:12 Q. **And you thought that was reasonable to do. Right?**
15:04:15 A. **I did.**
15:04:15 Q. **Because you would anticipate that Berinert would treat**
15:04:19 **all the manifestations of HAE. Correct?**
15:04:22 A. **Yes.**
15:04:23 Q. **That is what they had been doing with it in Europe for**
15:04:27 **30 years by 2009. Right?**
15:04:29 A. **Yes.**
15:04:29 Q. **In fact, you know, there was research published before**
15:04:34 **Firazyr was approved in the United States that said just**
15:04:37 **that about Berinert. Right?**
15:04:38 A. **Yes.**
15:04:39 Q. **And if you turn in your binder to DTX-76, this is a**
15:04:55 **paper by Timothy Craig entitled Prospective Study of Rapid**
15:04:59 **Relief Provided By CI Esterase Inhibitor in Emergency**
15:05:03 **Treatment of Acute Laryngeal Attacks in HAE.**
15:05:07 **Right?**
15:05:08 A. **Correct.**
15:05:08 Q. **And C1 esterase inhibitor is Berinert?**
15:05:13 A. **It is.**

15:05:13 Q. **And Timothy Craig is well known in the research area?**

15:05:17 A. **Good.**

15:05:17 Q. **Well respected guy?**

15:05:19 A. **Yes, clinical work is what he does.**

15:05:21 Q. **This is published 2010. Right?**

15:05:27 A. **Right. So this is published subsequent to the initial approval of Berinert but before the subsequent approval.**

15:05:32 Q. **Correct. If we look just at the conclusion here, in the abstract, it says, "Berinert concentrate is an effective and safe emergency treatment for providing reliable and rapid relief from the potentially life-threatening symptoms of laryngeal HAE attacks."**

15:05:48 **Correct?**

15:05:48 A. **Correct.**

15:05:49 Q. **That was known about Berinert before Firazyr was approved in the United States. Right?**

15:05:54 A. **Correct.**

15:05:54 Q. **And you agree with that?**

15:05:58 A. **I agree with that. Not yet approved at that point because, one has to make one assumption in 2009, that was because, if you remember, in the original study, it was used open label. And they had a certain number of patients with laryngeal attacks even in that study. Now, I am not at the FDA. I have to assume that the FDA felt that it was just an insufficient number to allow them approval at that point in**

15:06:28 time. So they added to it in the ensuing two years and then
15:06:33 subsequently got the approval.
15:06:34 Q. You are familiar with Konrad Bork?
15:06:36 A. Yes, he is a friend of mine.
15:06:38 Q. Who is he, besides being a friend of yours?
15:06:40 A. He resides in Germany and he is a very fine HAE
15:06:46 researcher.
15:06:46 Q. He published about using Berinert in laryngeal attacks
15:06:50 in Europe well before 2009. Correct?
15:06:54 A. It is true.
15:06:54 Q. He also published about patients self-administering
15:06:57 Berinert in Europe before 2009. Right?
15:07:01 A. He did.
15:07:01 Q. And that was well known to doctors who treated HAE
15:07:05 patients as well. Right?
15:07:06 A. Yes.
15:07:20 Q. Now, I think you agreed that Berinert was actually
15:07:25 approved for self-administration in December of 2011.
15:07:29 Right?
15:07:29 A. Yes.
15:07:29 Q. So that's just three months after Firazyr is approved.
15:07:33 Correct?
15:07:34 A. Yes.
15:07:34 Q. So there was a three month period where Firazyr was on
15:07:38 the market and the only FDA-approved drug for

15:07:41 **self-administration treatment acute attacks of HAE. Right?**

15:07:46 A. **Right.**

15:07:46 Q. **By December 2011 --**

15:07:48 A. **But the only one for self-administration plus subcu.**

15:07:53 Q. **Understood. But Kalbitor was subcu?**

15:07:57 A. **Right.**

15:07:57 Q. **I think you said you could call Dyax and they would send somebody over to help administer it. Right?**

15:08:03 A. **Right.**

15:08:03 Q. **So you could get it on board pretty quickly even though you needed a health care provider?**

15:08:09 A. **It's all relative. That one, the black box is a big caveat, because as simple as it seemed, you couldn't self-inject it. That was a very disappointing thing for we in the field in 2009, as well as Dyax.**

15:08:40 Q. **Dr. Kaplan, I want to look for a moment at one of your slides, PDX2.4. This was the summary of your opinions you provided.**

15:09:01 A. **Yes.**

15:09:01 Q. **The first opinion you had is as of 1989 there was a need for a safe, effective, and convenient treatment for acute attacks of HAE. Right?**

15:09:10 A. **Correct.**

15:09:11 Q. **It is not your opinion that Firazyr met that need in 1989. Correct?**

15:09:15 A. **Correct.**

15:09:15 Q. **Your opinion is that Firazyr met that need when it was FDA-approved in the United States in 2011. Correct?**

15:09:20 A. **Correct.**

15:09:23 Q. **And so you agree that although your second opinion is that Firazyr met the need, Firazyr was not the first drug to meet the need that you have identified. Right?**

15:09:28 A. **Firazyr -- well, let's be specific. Kalbitor, I wouldn't give it the safety award because of the black box.**

15:09:34 Q. **Kalbitor you mean?**

15:09:39 A. **Yes, I am sorry. And Berinert neither was safe, effective, and I would put "convenient" in quotation marks because if you are not subcutaneous, you can't compare it to somebody who requires an IV for administration of the medication.**

15:09:43 **But at the time, it was sure a big step in the right direction.**

15:09:46 Q. **Now, when we talk about Firazyr here, we are not just talking about icatibant. Correct?**

15:09:49 A. **I am.**

15:09:54 Q. **We are talking about icatibant in its syringe and formulated. Right?**

15:09:57 A. **Yes.**

15:10:02 Q. **And you know that it's icatibant acetate that they use. Correct?**

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15:10:26 A. **It is. It is a solution of salt and they make up an**
15:10:31 **acetate by mixing two things.**
15:10:32 Q. **You are not an expert in that formulation work.**
15:10:34 **Correct?**
15:10:35 A. **I don't do formulation but I certainly know what that**
15:10:37 **stuff is.**
15:10:38 Q. **But you don't know how hard it was or how much work**
15:10:41 **Shire or Hoechst or --**
15:10:44 A. **Oh, no. We know a lot of work went into it.**
15:10:47 Q. **They did a lot of work on that formulation to come up**
15:10:51 **with the convenient treatment that is now Firazyr. Right?**
15:10:53 A. **The convenient aspect is the fact that it is highly**
15:10:56 **soluble, stable at room temperature and can be preloaded and**
15:11:00 **it's all good.**
15:11:01 Q. **But they had to do a lot of work beyond just having**
15:11:04 **icatibant. Correct?**
15:11:06 A. **Absolutely.**
15:11:09 Q. **It's all that work combined together, the molecule and**
15:11:12 **the work on the formulation and the syringe, that makes it a**
15:11:16 **convenient treatment?**
15:11:17 A. **Yes. That's fair.**
15:11:22 Q. **You don't know if the patent actually even talks about**
15:11:26 **icatibant acetate, the patent we are here for at this trial.**
15:11:29 **Right?**
15:11:29 A. **I do not know.**

15:11:31 Q. **You have been in the courtroom for some of the**
15:11:35 **testimony?**
15:11:38 A. **Today, yes. Yesterday not. I heard the opening**
15:11:41 **statements. Today I heard part of it.**
15:11:43 Q. **Sir, have you seen the patent now as part of the**
15:11:46 **trial?**
15:11:46 A. **I did. But I didn't take in much.**
15:11:49 Q. **Before coming to court for the trial, you never had**
15:11:53 **even looked at the patent that is at issue in this case.**
15:11:56 **Right?**
15:11:57 A. **That's correct.**
15:12:11 Q. **Dr. Kaplan, if you could turn in your binder to**
15:12:19 **DTX-84. You are familiar with this article, sir?**
15:12:25 A. **Yes.**
15:12:25 Q. **It is a WAO Guideline for the Management of Hereditary**
15:12:31 **Angioedema. Right?**
15:12:32 A. **Yes.**
15:12:32 Q. **If we look at the bottom of the first page, it was**
15:12:36 **published in December 2012. Correct?**
15:12:39 A. **Correct.**
15:12:39 Q. **This is what's called the consensus guideline. It's a**
15:12:42 **group of doctors who are experts in the field, get together**
15:12:45 **and decide how to direct people to treat patients with HAE.**
15:12:50 **Right?**
15:12:50 A. **Yes. It's one of a number of them. But that's fine.**

15:12:55 Q. **You actually participated in this one. Right?**

15:12:58 A. **Yes, somewhere. If I did, my name is there. I don't see my name in this one.**

15:13:03 Q. **On the second page, in the top left-hand corner, six or seven down, Allen Kaplan?**

15:13:10 A. **There I am.**

15:13:10 Q. **So you participated in this one?**

15:13:12 A. **I did.**

15:13:12 Q. **You helped to draft this guideline?**

15:13:14 A. **Yes.**

15:13:14 Q. **You reviewed it before it was published?**

15:13:16 A. **Yes.**

15:13:17 Q. **You agreed with this when it was published?**

15:13:19 A. **Yes.**

15:13:20 Q. **Let's look at a couple of the details here. If we turn to DTX-84-7. It would be on the right-hand side, Therapy of HAE and On-Demand Treatment. So that's the acute attacks. Correct?**

15:13:36 A. **Yes.**

15:13:36 Q. **And the On Demand Treatments for acute attacks. Right?**

15:13:42 A. **Right.**

15:13:42 Q. **And if we look at Recommendation 4, and we pull that out, this is what you and the other experts were recommending as the treatments. Correct?**

15:13:50 "We recommend that HAE attacks are treated with
15:13:53 C1-INH, kallikrein, or icatibant."
15:13:59 Right?
15:13:59 A. Right.
15:14:00 Q. And CI-INCH is Berinert. Correct?
15:14:03 A. Correct.
15:14:04 Q. And ecallantide is Kalbitor. Correct?
15:14:07 A. Correct.
15:14:07 Q. And there was no differentiation, it was either, just
15:14:12 pick one of these three. Right?
15:14:14 A. Yes. Parenthetically, in writing guidelines, I mean,
15:14:18 there is no favoritism for one pharmaceutical or another.
15:14:21 You will see that throughout. They are listed as choices.
15:14:27 Some of the evidence is weighed. But ultimately the choice
15:14:30 is made by the physician and patient as to which one they
15:14:33 are going to use.
15:14:34 Q. And the guidelines here didn't suggest any one of
15:14:37 these was better or worse than any other?
15:14:40 A. No. We didn't and wouldn't.
15:14:41 Q. If we go to 84-11, and Recommendation 13 on the
15:14:47 right-hand side, we pull that out. This is specifically
15:14:51 talking about treating children?
15:14:55 A. Yes.
15:14:55 Q. Here only one drug is recommended?
15:14:58 A. Yes.

15:14:58 Q. **And it's Berinert?**
15:15:01 A. **Yes.**
15:15:02 Q. **And if we turn to the next page, Recommendation 14. This is the recommendation for treating pregnant and lactating women. Correct?**
15:15:11 A. **Correct.**
15:15:11 Q. **Again, it's only one drug that is recommended. Right?**
15:15:14 A. **Correct.**
15:15:14 Q. **And it's Berinert. Correct?**
15:15:16 A. **Correct.**
15:15:17 Q. **And if we go then to the next page, 84-14, if we pull out Table 3 at the bottom, this is the summary you all provided. Correct?**
15:15:30 A. **Yes.**
15:15:30 Q. **And first on the list is Berinert. Right?**
15:15:33 A. **Right.**
15:15:33 Q. **And for efficacy it gets three little pluses. Right?**
15:15:37 A. **Yes.**
15:15:37 Q. **And for safety it gets three little pluses. Right, which is the best you can get?**
15:15:43 A. **It looks like that, I see no fours, I am assuming this was one to three.**
15:15:47 Q. **And two up from the bottom is icatibant. Right?**
15:15:50 A. **Right.**
15:15:50 Q. **It also gets the three little pluses for efficacy and**

15:15:54 **the three little pluses for safety?**

15:15:56 A. **Correct.**

15:15:56 Q. **And the bottom one is Kalbitor or ecallantide, that also has three little pluses for efficacy?**

15:16:03 A. **Right.**

15:16:06 Q. **And three little pluses for safety. Right?**

15:16:06 A. **Right.**

15:16:08 Q. **And there is no difference in this guideline that you helped write between Berinert, icatibant and ecallantide. Right?**

15:16:09 A. **Right.**

15:16:18 Q. **But Berinert and kallikrein were approved in the United States before icatibant. Right?**

15:16:18 A. **Yes.**

15:16:22 Q. **And Berinert was in fact used as early as the 1970s to treat acute attacks of HAE?**

15:16:23 A. **Yes.**

15:16:23 **MR. WIESEN: Your Honor, can I just have a moment?**

15:16:28 **(Pause.)**

15:16:31 **MR. WIESEN: No further questions, Your Honor.**

15:16:35 **THE COURT: Mr. Blumenfeld.**

15:16:38 **REDIRECT EXAMINATION**

15:16:39 **BY MR. BLUMENFELD:**

15:16:41 Q. **Just a few more questions, Dr. Kaplan.**

15:16:43

15:16:44

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15:16:57

15:17:02 **When another treatment was approved in 2009, was there still a need for Berinert treatment for acute attacks of HAE?**

15:17:11 A. **Right. My opinion is that there was. And that is notwithstanding the fact that Berinert was a fine addition and created considerable enthusiasm.**

15:17:25 **Before -- at that point, when it first came out, we didn't even know it was possible to have a subcutaneous administered drug. Kalbitor came out soon thereafter and there it was. And anyone who saw that felt, gee, if -- this is a good way to go. But it had the black box. So looking at those two, I would say, okay, the ideal from a variety of perspectives would be to have something that's subcutaneous, ultimately self-administered, fast, and safe, and that would be about as good as you could do. I felt there was still a need.**

15:18:06 Q. **Is there any question that Firazyr can be administered more quickly than Berinert?**

15:18:14 A. **There is no question about that.**

15:18:15 Q. **And is there an advantage to fast administration?**

15:18:22 A. **We alluded to that twice, in different contexts. You remember, even in the study where it was shown, they looked at one hour, two-hour, three-hour, and you could argue that you would like to look at even faster times. But the perception in general is that the faster you get it in, the**

15:18:43 better the response, and it just stands to logic that you
15:18:50 are going to get it in faster when you self-administer it
15:18:55 with a preloaded syringe, so it's a matter of seconds before
15:19:00 you have started the process.
15:19:01 Then it's the time in which it diffuses through
15:19:04 the skin to get into your bloodstream, which is estimated to
15:19:07 be 20 to 30 minutes. If you stop an attack, in under an
15:19:12 hour and something that last 48 hours, you have really done
15:19:16 something well.
15:19:17 Q. Can you put up JTX-21, the Berinert label. If you
15:19:24 turn to Pages, I think it's 5 and 6. Let me take a look at
15:19:44 that and make sure I have the right page.
15:19:47 Page 3 and then Page 4.
15:19:52 A. 21.--
15:19:53 Q. .3. Start there.
15:19:57 A. Okay.
15:19:57 Q. This is a chart that shows how to reconstitute
15:20:03 Berinert. I don't want you to go into a long explanation.
15:20:06 But briefly, what does the patient or the health care
15:20:11 provider have to do in order to prepare the Berinert for
15:20:15 intravenous administration?
15:20:17 A. Well, you could read down. Before you have gotten the
15:20:22 IV in, you have a vial of Berinert, it is a solid, so it is
15:20:29 a powder at the bottom of the bottle, you have a sterile
15:20:34 vial. It is at room temperature, saying using good

15:20:36 technique means in sterile gloves and whatever you have
15:20:39 available.
15:20:39 Place the barrel of the vial, mix them, set it
15:20:42 on a flat surface, remove the flip stops, open the vial
15:20:46 stopper, swab it with alcohol, allow it to dry, open the
15:20:50 vial to mix, the same sort of thing, peel away the lid, set
15:20:55 it in the package, place the diluent on a flat surface, then
15:20:59 grip the vial transfer set together with clear passage, snap
15:21:04 it -- snap the blue of the mixed two vial transfer set onto
15:21:12 the diluent vial stopper at a 90-degree angle.
15:21:14 They give you a picture. Remove the clear
15:21:17 passage from the vial transfer set. Make sure you only pull
15:21:20 up on the clear passage and not the vial transfer set.
15:21:22 With the vial dry firmly on a flat surface,
15:21:26 invert it, set it attached, snap the transparent adapter,
15:21:31 blah, blah, blah.
15:21:32 The diluent would automatically transfer, it
15:21:33 goes on and it goes on and on.
15:21:36 It's a process to -- you got to get the fluid
15:21:42 into the diluent. Shake it up a little bit. Then move it
15:21:44 out. Then you have to start your IV. Then you hang this
15:21:48 thing up onto the IV. And you administer it at a rate
15:21:51 that's about 4 ml's per minute. So it takes two and a half
15:21:58 minutes to get it in.
15:21:59 Q. Is this easy for a patient who is under an acute

15:22:03 **attack to do?**

15:22:04 A. **First of all, patients are instructed on how to do it.**
15:22:07 **But it is not simple and it takes practice. You have to**
15:22:10 **work on it. I am always concerned that if you are having an**
15:22:13 **attack and your hands are swollen, you have got some**
15:22:15 **problems.**

15:22:15 Q. **Dr. Kaplan, for the patient who self-administers**
15:22:21 **Firazyr, what do they have to do?**

15:22:24 A. **Oh, self-administering Firazyr, that is like it was**
15:22:28 **sitting over here. You obviously put it in a place where**
15:22:31 **you have reasonable access. You grab it, and you stick it**
15:22:35 **in. You have to just be able to stick it in and pull the**
15:22:40 **plunger. It's seconds.**

15:22:42 Q. **One more question. If you turn to your**
15:22:44 **cross-examination notebook, DTX-84, turn to Page 84-00007,**
15:22:56 **Mr. Wiesen asked you about some of the recommendations.**
15:22:59 **What is Recommendation No. 3?**

15:23:02 A. **Tell me again?**

15:23:04 Q. **84-0007.**

15:23:07 A. **I will read it from there.**

15:23:09 **"We recommend that attacks are treated as early**
15:23:12 **as possible. Evidence grade: D. Strength of**
15:23:16 **recommendation: Strong."**

15:23:19 **So that relates to what I had said, in general,**
15:23:25 **the faster the better, and my position has been, regardless**

15:23:31 of all the stuff that we went over today, my personal
15:23:34 position, based on everything I know, is that the faster you
15:23:38 get it in, the better it is, and icatibant, I think, is the
15:23:43 one that allows you to do that acutely with the most
15:23:47 facility and rapidity.
15:23:50 MR. BLUMENFELD: Thank you, Dr. Kaplan.
15:23:51 THE COURT: Thank you, Doctor. Please be
15:23:53 careful stepping down. You are excused.
15:23:56 (Witness excused.)
15:23:59 THE COURT: We will take a stretch.
15:24:02 (Recess taken.)
15:38:03 THE COURT: All right. Take your seats, ladies
15:38:05 and gentlemen. Let's continue.
15:38:07 Counsel?
15:38:09 MS. KUZMICH: Good afternoon, Your Honor.
15:38:10 Plaintiffs call Dr. Klaus Wirth as a fact witness in an
15:38:14 individual capacity.
15:38:15 Dr. Wirth was an employee at Hoechst in the
15:38:20 mid-1980s, when icatibant was invented. He's also an
15:38:25 inventor on the '7,803 patent.
15:38:27 THE COURT: All right.
15:38:27 MS. KUZMICH: Dr. Wirth?
15:38:29 THE COURT: Why are we referring to the '803 as
15:38:32 the '7,803?
15:38:33 MS. KUZMICH: Your Honor, because there's a

15:38:35 piece of prior art that's actually the '803 patent.
15:38:37 THE COURT: All right.
15:38:38 MS. KUZMICH: So there has been some confusion
15:38:40 and this is how we resolved it.
15:38:42 THE COURT: Okay. I was wondering. Is this a
15:38:44 new term of art?
15:38:47 MR. WIESEN: I think Mr. James had referred to
15:38:49 the '5,803 at some point. That was the first one that came
15:38:52 up.
15:38:52 THE COURT: Okay. Couldn't tell. Sorry about
15:38:54 that, Doctor. He's going to swear you.
15:38:56 ... KLAUS WIRTH, having been duly
15:39:05 sworn as a witness, was examined and testified as
15:39:10 follows ...
15:39:20 MS. KUZMICH: Your Honor, may I approach with
15:39:21 binders?
15:39:22 THE COURT: Sure.
15:39:23 MS. KUZMICH: Thank you.
15:39:42 (Ms. Kuzmich handed binders to the Court and to
15:39:44 the witness.)
15:39:56 DIRECT EXAMINATION
15:39:57 BY MS. KUZMICH:
15:40:19 Q. Dr. Wirth, good afternoon. Would you please state
15:40:22 your full name for the record?
15:40:24 A. My name is Klaus Wirth.

15:40:26 Q. **Dr. Wirth, what is your current occupation?**

15:40:30 A. **I'm currently a pharmacologist at Sanofi Aventis Deutschland. I'm a research scientist in the laboratory.**

15:40:38 Q. **How long have you been employed by Sanofi Aventis Deutschland?**

15:40:42 A. **I have been employed by Sanofi Aventis Deutschland since it became this entity, and I have been employed by the predecessor company since 1984, which initially was Hoechst.**

15:40:59 Q. **Would you please describe your education since graduating from the German equivalent of high school?**

15:41:04 A. **I have an MD from 1993. Twelve years ago, I received an additional degree. It's a qualification for professorship in pharmacology from the University of Frankfurt. And I'm also teaching students, medicinal students at the University of Frankfurt. I'm board-certified in medicine for pharmacology. I'm instructor for pharmacology and I'm also an examiner of certification.**

15:41:43 Q. **Dr. Wirth, after you received your M.D., what did you do?**

15:41:47 A. **I spent one year in hospitals in Germany practicing internal medicine.**

15:41:54 Q. **And after practicing medicine for one year, what did you do then?**

15:41:58

15:41:59 A. **In 1984 I joined Hoechst.**

15:42:05 Q. **Would you please describe generally your responsibilities at Hoechst when you joined them in 1984.**

15:42:09 A. **I joined Hoechst as a pharmacologist. I was responsible for designing and performing in vitro and in vivo pharmacologic studies.**

15:42:25 Q. **Dr. Wirth, did your responsibilities change over time at Hoechst?**

15:42:30 A. **Yes. I worked in different fields. I started in biotechnology, where I was one year. Then I went into general pharmacology for six months. Then I spent two to three years in gastroenterology pharmacology. And then I switched from experimental pharmacology to clinical pharmacology for my board certification. And after this year, I changed again to cardiovascular experimental pharmacology.**

15:43:03 Q. **And what were some of the projects that you were involved in when you returned to Hoechst after receiving your board certifications and joining cardiovascular pharmacology?**

15:43:15 A. **When I returned, I took over the bradykinin antagonist project.**

15:43:22 Q. **And, Dr. Wirth, if you can recall, when did you actually become involved in the bradykinin antagonist project?**

15:43:28 A. **It was at some time between 1989 and 1990.**

15:43:35 Q. **Were you involved in Hoechst's bradykinin antagonist project from its inception?**

15:43:42 A. **No.**

15:43:43 Q. **When you joined Hoechst's bradykinin antagonist team, what role did you play?**

15:43:44 A. **I took over a role in which I was responsible for performing, designing and collecting the pharmacologic data, and I was also responsible for monitoring the scientific literature.**

15:43:48 Q. **How long were you part of the bradykinin antagonist project at Hoechst?**

15:43:49 A. **As long as it existed.**

15:43:55 Q. **Did your role in the bradykinin antagonist project change over time?**

15:44:01 A. **Yes, it changed. In the beginning we had to perform the necessary pharmacologic studies, and at a point in time, these studies had been finished. And then there was a push to develop the compound, and then my role changed and I have been advisor to the development department, toxicology, formulation, and doing the studies. And I was also strongly involved in the contacts with general scientists.**

15:44:04 Q. **Dr. Wirth, if you would please turn to JTX-01 in your binder. And we're going to project the documents on the screen today as well, Dr. Wirth.**

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15:45:08 **And if you look at JTX-01, do you recognize this**
15:45:10 **document?**
15:45:11 A. **Yes.**
15:45:11 Q. **How do you recognize this document?**
15:45:13 A. **I have seen it, I have seen it in preparation, and I**
15:45:18 **can't remember having seen it before. I have seen so many**
15:45:20 **documents, I may have seen before, I can't remember. I have**
15:45:24 **seen it during the preparation.**
15:45:25 Q. **Dr. Wirth, is it acceptable to you if we refer to the**
15:45:29 **patent then as JTX-01 on the screen as the '333 patent?**
15:45:33 A. **Yes.**
15:45:34 Q. **Dr. Wirth, please turn your attention to Claim 14 of**
15:45:41 **the '333 patent. Now, that's going to be at JTX-01.24, and**
15:45:47 **that's at column 44, line 44 through 46. We're going to**
15:45:51 **project that on the screen.**
15:45:52 **Do you recognize the peptide of claim 14 of the**
15:45:56 **'333 patent?**
15:45:57 A. **Yes.**
15:45:57 Q. **And what is that peptide?**
15:45:59 A. **It is Hoe 140, also called icatibant.**
15:46:05 Q. **So if we refer to Hoe 140 or icatibant, do you**
15:46:09 **understand them to mean the same thing?**
15:46:10 A. **Yes.**
15:46:11 Q. **Dr. Wirth, please turn to PTX-12. And PTX-12, do you**
15:46:23 **recognize this document?**

15:46:24 A. **Yes.**

15:46:25 Q. **And what is PTX-12?**

15:46:26 A. **It's the so, the so-called green file. This is the**
15:46:31 **document in which we have to document, collect**
15:46:35 **pharmacological and biochemistry data. The document served**
15:46:41 **for registration and submission to the regulatory**
15:46:46 **authorities.**

15:46:47 Q. **Was the data in PTX-12 generated by Hoechst?**

15:46:50 A. **Yes.**

15:46:51 Q. **Were you involved with generating data contained in**
15:46:55 **PTX-12?**

15:46:56 A. **Yes.**

15:46:56 Q. **Were you involved in the creation of the document**
15:47:00 **labeled PTX-12?**

15:47:01 A. **Yes. I compiled pharmacologic data.**

15:47:05 Q. **Would the data recorded in PTX-12 have been recorded**
15:47:12 **in some form about the time the data was generated?**

15:47:15 A. **Yes.**

15:47:16 Q. **Would PTX-12 have been created at or about the time**
15:47:18 **the data contained in it was generated?**

15:47:22 A. **Reports in the document was generated at some time**
15:47:25 **after, after the experiments, because an official decision**
15:47:33 **was needed to write these reports. Such reports are only**
15:47:36 **written after, in a document after more development.**

15:47:43 Q. **Was the data generated in PTX-12 maintained in**

15:47:49 **Hoechst's ordinary course of business?**

15:47:50 A. **Yes.**

15:47:50 Q. **Dr. Wirth, please turn to page PTX-012.24. And we're going to call that up on the screen.**

15:48:00 **Do you recognize this document, Dr. Wirth?**

15:48:05 A. **Yes.**

15:48:06 Q. **What is this document?**

15:48:07 A. **It reports the efficacy of Hoe 140 in the isolated guinea pig pulmonary arteries constricted within bradykinin.**

15:48:19 Q. **What is the date of this report?**

15:48:20 A. **September 5th, 1989.**

15:48:23 Q. **When were the data in this report generated?**

15:48:28 A. **Generated in the investigational period, which is January 1989.**

15:48:35 Q. **Dr. Wirth, in the title of this report there appears the language, D-Arg [HYP2Thi5,8D-Phe-7]-BK. Do you know what that stands for?**

15:48:47 A. **Yes.**

15:48:48 Q. **What does that stand for?**

15:48:49 A. **It's a bradykinin antagonist and it is reported in the literature.**

15:48:54 Q. **Dr. Wirth, please turn to page PTX-012.27.**

15:49:06 **Dr. Wirth, do you have an understanding of what the data mean that are shown in the table on PTX-012.27?**

15:49:14 A. **The data that the figure shows, concentration response**

15:49:20 curve for Hoe 140 and this literature, the compound,
15:49:29 [Hyp2,Thi5,8.D-Phe7] 5867. Again, bradykinin constriction.
15:49:36 On the left-hand side we see the concentration
15:49:40 curve for Hoe 140. On the right-hand side you see for the
15:49:45 other compound. And what you see is what is calculated out
15:49:49 of, out of these, out of this curve. It's the so-called IC
15:49:54 50 value which reflects the activity. For Hoe 140 it's 5.4
15:50:05 times ten to the minus nine molar. For the other compound
15:50:08 it is 6.4 times ten to the minus six. It means that Hoe 140
15:50:14 is 100 to 1,000 fold more potent than any other compound.
15:50:22 Strongly superior.
15:50:24 Q. Excuse me, Dr. Wirth. If you would now turn to
15:50:28 PTX-01, again. And please refer specifically to Column 16.
15:50:36 And there's Table 1 that appears in Column 16. We're going
15:50:41 to have highlighted on the screen, because it's very hard
15:50:44 to see, the 18th peptide in Table 1, which we have
15:50:48 highlighted.
15:50:48 And do you recognize that peptide?
15:50:51 A. Yes. It is Hoe 140.
15:50:54 Q. Does the table of the '333, Table 1, report an IC 50
15:51:00 value for icatibant generated in the isolated guinea pig
15:51:05 pulmonary artery assay?
15:51:07 A. Yes. It's 5.4 times ten to the minus nine. It's the
15:51:12 same as we saw in the report filed.
15:51:16 Q. And so how do you know that the data that you saw in

15:51:19 **the green file, JTX 12, is the same data that we're looking**
15:51:23 **at in Table 1 of the '333 patent?**
15:51:25 **THE COURT: Yes?**
15:51:27 **MR. WIESEN: I'm going to object that there's a**
15:51:28 **lack of foundation. He testified he wasn't sure he had even**
15:51:31 **seen the patent before he started preparing for this case,**
15:51:34 **so I've let Ms. Kuzmich run through the document, but asking**
15:51:38 **him how he knows that is the source of the data, he began by**
15:51:42 **saying he has no foundation for that testimony.**
15:51:45 **MS. KUZMICH: Your Honor, in his deposition he**
15:51:47 **actually testified specifically to Table 1 that we're**
15:51:50 **looking at here and said that that is the IC 50 at 5.4 times**
15:51:55 **ten to the minus nine for icatibant. And he also then**
15:51:59 **testified later --**
15:52:00 **THE COURT: That's a prior consistent statement,**
15:52:01 **not a prior -- that's not a proper use of the deposition,**
15:52:04 **counsel. Sustained.**
15:52:23 **BY MS. KUZMICH:**
15:52:23 Q. **Dr. Wirth, if you could turn to your binder PTX-28.**
15:52:43 **Dr. Wirth, the title of the article is New and Highly Potent**
15:52:47 **Bradykinin Antagonists.**
15:52:48 **Are you an author on this publication?**
15:52:50 A. **Yes.**
15:52:50 Q. **Would you please describe generally the information in**
15:52:54 **this publication?**

15:52:56 A. **The paper reports the main in vitro and in vivo**
15:52:59 **pharmacology data for HOE140.**
15:53:05 Q. **As an author on this publication, PTX-28, what was**
15:53:10 **your role in generating the data that is provided therein?**
15:53:16 A. **I was involved in generating experimental data and**
15:53:18 **experiments and I wrote the pharmacological part of this**
15:53:21 **paper.**
15:53:22 Q. **Dr. Wirth, where is the pharmacological data presented**
15:53:26 **in this article?**
15:53:27 A. **There are two figures towards the end. The figure on**
15:53:33 **top, on the top shows the main in vitro finding, the**
15:53:41 **activity against bradykinin in different isolated organs of**
15:53:45 **different species and it shows PA2 values between 8 and 9,**
15:53:49 **which indicates a very high potency. The higher the PA2,**
15:53:53 **the more potent are the compounds.**
15:53:55 **So the compound is almost uniformly effective in**
15:53:59 **all these different species and organs, with one exception.**
15:54:03 **It is the rabbit aorta -- it is not affected from the rabbit**
15:54:10 **aorta because you have subtype receptor B1 in rabbit aorta,**
15:54:16 **an HOE 140 is a B2 receptor antagonist.**
15:54:20 Q. **Dr. Wirth, if you could briefly describe below what is**
15:54:24 **being shown in Figure 3?**
15:54:25 A. **It shows bradykinin induced constriction in a guinea**
15:54:30 **pig. The two lower curves show the potency of HOE140**
15:54:38 **inhibits this constriction. And even at a low dose, as low**

15:54:43 as 100 picomole per kilogram, HOE 140 almost abolishes the
15:54:52 constriction of bradykinin.
15:54:53 So this shows the high potency in vitro. So
15:54:56 it's very potent in vitro, what you see above, and below you
15:55:01 see that it can be translated into a high in vivo potency.
15:55:05 Q. Dr. Wirth, if you could please turn to DTX-50. DTX-50
15:55:18 is an article titled "HOE140, A New Potent and Long Acting
15:55:24 Bradykinin Antagonist: In vivo Studies." Are you the first
15:55:28 author on this article?
15:55:33 A. Yes.
15:55:34 Q. Can you please describe the purpose of this article?
15:55:36 A. The paper shows the in vivo studies with HOE140, which
15:55:41 here are shown the main findings of the pharmacology of
15:55:48 HOE140.
15:55:49 Q. Doctor, what compounds were evaluated in DTX-50?
15:55:55 A. Two compounds, HOE140 and the original compound we
15:55:59 already talked about, D-Arg-Hyp-2, Thi-5,8, D-Phe-7
15:56:06 bradykinin.
15:56:06 Q. Dr. Wirth, would you please turn to DTX-107. DTX-107
15:56:19 an article Titled HOE140 a New Potent and Long Acting
15:56:23 Bradykinin Antagonist: In vitro Studies.
15:56:26 Dr. Wirth, are you an author on this article?
15:56:29 A. Yes.
15:56:30 Q. Would you briefly describe or summarize the purpose of
15:56:33 this article?

15:56:34 A. **The paper shows and reports the in vitro efficacy of HOE140.**

15:56:40 Q. **What were the compounds that were evaluated in DTX-107?**

15:56:45 A. **Again, it was HOE140 and the bradykinin antagonist from the literature, the D-Arg[Hyp2Thi5,8D-Phe-7]BK.**

15:56:51 Q. **Dr. Wirth, would you please turn --**

15:56:57 **THE COURT: Counsel, before we dive too far, lets me see you at sidebar.**

15:57:00 **(The following took place at sidebar.)**

15:57:02 **THE COURT: I want to revisit my ruling earlier. I think we are all aware of 608(b)(1)(a). So I wanted to talk about it.**

15:57:03 **Go ahead.**

15:59:06 **MS. KUZMICH: I believe this is where you have sustained counsel's objection. Doctor Wirth testified in his deposition that he had possibly seen the patent during his work and then he said he also saw the patent before he prepared for his deposition and so --**

15:59:06 **THE COURT: He made a statement at the deposition.**

15:59:06 **MS. KUZMICH: He made that statement at the deposition while under oath.**

15:59:06 **MR. WIESEN: He was a Rule 30(b)(6) designee. So he was prepared specifically by counsel on certain**

15:59:06 **issues. We asked them before they brought him today, are we**
15:59:06 **going by 30(b)(6) so he could have been prepared or is he**
15:59:06 **here as an individual. They specifically said, as an**
15:59:06 **individual. I think that's the distinction here that**
15:59:06 **matters.**
15:59:06 **In the end, if that's the only question she**
15:59:06 **wants -- I didn't want us to get too far into --**
15:59:06 **THE COURT: Is that addressed?**
15:59:06 **MS. KUZMICH: That is the only question I was**
15:59:06 **connecting between the PTX-12 document and the patent. I**
15:59:06 **guess, counsel, I thought when he said in his deposition**
15:59:06 **that he had possibly seen the patent before, I don't think**
15:59:06 **that was completely just the deposition. That's where I was**
15:59:06 **coming from.**
15:59:06 **MR. WIESEN: If that's all she wants. The**
15:59:06 **numbers match up.**
15:59:06 **THE COURT: I will let you ask the question.**
15:59:06 **(End of sidebar conference.)**
15:59:08 **THE COURT: Counsel, you can re-put the**
15:59:10 **question.**
15:59:11 **MS. KUZMICH: Thank you.**
15:59:12 **BY MS. KUZMICH:**
15:59:12 Q. **Dr. Wirth, if you would turn to JTX-01, that is the**
15:59:19 **'333 patent again. If we could go to Column 16 and Table I.**
15:59:23 **And we can highlight the 18th peptide down. If we could**

15:59:34 highlight that on the screen, please.

15:59:38 My question to you, Dr. Wirth, was you

15:59:41 identified this peptide as icatibant. My question to you

15:59:47 was how did you know these data that you had in the '333

15:59:53 data for icatibant are the same as the data we saw in the

15:59:56 Green file, which was PTX-12?

15:59:59 A. This is exactly the same value, IC_{50} value, and it is

16:00:04 the pulmonary artery, and it is the same code, same formula.

16:00:08 So it is identical.

16:00:15 Q. Dr. Wirth, we are going to go back to where we were,

16:00:20 which is PTX-062. If you could turn in your binder to that.

16:00:32 Dr. Wirth, so you know, that has been translated into

16:00:34 English and the English version appears at PTX-062T.

16:00:44 Dr. Wirth, do you recognize PTX-062?

16:00:49 A. Yes.

16:00:50 Q. And what is this document?

16:00:51 A. This is minutes from a research conference which is

16:00:57 called Gordon Conference on Kinins and Kallikreins held in

16:01:07 1993 in Ventura, California.

16:01:12 Q. The name on the top left of the document PTX-062T,

16:01:18 that is Professor B. Scholkens. Do you recognize that name?

16:01:24 A. Yes. He was the head director of the department.

16:01:27 Q. Why would Dr. Scholkens's name be on the document?

16:01:30 A. Because he wrote the minutes.

16:01:31 Q. Did Dr. Scholkens attend this Gordon Conference in

16:01:35 **February of 1993 that is being referenced on this document?**

16:01:38 A. **Yes.**

16:01:39 Q. **Was it typical practice for a Hoechst scientist, such as Dr. Scholkens, to write reports on conferences they attended?**

16:01:48

16:01:49 A. **Yes. Of course, it was obligatory.**

16:01:51 Q. **Was it Hoechst's practice to distribute these reports?**

16:01:55 A. **Yes, and it was obligatory.**

16:01:56 Q. **Did Hoecsht maintain conference reports such as PTX-062 in its ordinary course of business?**

16:02:00

16:02:02 A. **Yes.**

16:02:03 Q. **Did you attend this conference described at PTX-062?**

16:02:09 A. **Yes.**

16:02:09 Q. **Would you have received a copy of PTX-062 at or about the time it was created?**

16:02:13

16:02:15 A. **Yes.**

16:02:15 Q. **If you would turn, Dr. Wirth, to Page PTX062T.3, and if you would focus your attention on the fifth and sixth sentences of the first paragraph on that page, and would you please read aloud those sentences which we are going to have highlighted?**

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16:02:37 A. **"A certain standstill has occurred in the area of synthesizing additional bradykinin antagonists. Companies such as Syntex, Sterling Winthrop and Nova have pulled out because their programs did not include any substances that**

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16:02:44

16:02:49

16:02:52 were superior to HOE140."
16:02:55 Q. Does the statement that you just read reflect your
16:02:59 recollection regarding the bradykinin antagonist competition
16:03:02 landscape as of February 1993?
16:03:05 A. Yes.
16:03:05 Q. If you would turn to Page PTX-062T.5. And if you
16:03:13 would please focus your attention on the last paragraph on
16:03:16 that page. Then please read aloud the sentences that have
16:03:20 been highlighted on the screen from that paragraph?
16:03:23 A. "The remarks of Steranka from Nova, which in the
16:03:28 meantime has discontinued its efforts in the area of
16:03:31 peptides, were particularly interesting. The company has
16:03:33 initiated a major shift in its previous orientation with a
16:03:38 so-called overall discovery program with the ultimate goal
16:03:42 to develop non-peptide BK antagonists."
16:03:50 Q. What is your understanding, if you know, of a
16:03:53 non-peptide bradykinin antagonists?
16:03:56 A. Non-peptide bradykinin antagonists are not composed of
16:04:01 amino acids, only of so-called heterocycles.
16:04:06 Q. Dr. Wirth, do you have any reason to doubt the
16:04:08 accuracy of the reporting in PTX-062 of the status of Nova's
16:04:16 bradykinin antagonist program?
16:04:17 A. No.
16:04:19 Q. Dr. Wirth, if you would please turn to PTX-064.
16:04:24 Again, I will note that PTX-064T is the English translation

16:04:31 **of PTX-064. Dr. Wirth, do you recognize PTX-064?**

16:04:40 A. **Yes.**

16:04:40 Q. **How do you recognize PTX-064?**

16:04:43 A. **This is a document I prepared and maintained. The entries made are the investigators, the name of the investigators who received HOE140, the purpose for which they requested HOE140, the amount and the date when the sample was sent off.**

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16:05:07 Q. **Dr. Wirth, when did you create this document?**

16:05:12 A. **After the first -- after I received the first request, when I noticed that there was a need to have such a document.**

16:05:19

16:05:22

16:05:22 Q. **Do you recall who the first investigator was to request a sample of HOE140 that was included on PTX-064?**

16:05:25

16:05:31 A. **Yes. It was Professor Werner Muller-Esterl, from the University of Mainz.**

16:05:36

16:05:37 Q. **Dr. Wirth, would you please turn to PTX-064T.46. Dr. Wirth, what is being shown on this page?**

16:05:48

16:05:52 A. **The first name that appears is indeed Werner Muller-Esterl, he received a sample of HOE140, the first one, five milligrams, on September 6, 1989.**

16:06:01

16:06:04

16:06:09 Q. **And about how many samples, based on PTX-064, were given to investigators of HOE140?**

16:06:21

16:06:24 A. **About 400.**

16:06:25 Q. **Was it common for more than 400 investigators or 400**

16:06:28 **investigators or so to have been interested in receiving**
16:06:32 **samples of compounds developed by Hoechst?**
16:06:34 A. **It was absolutely unusual, and I have never seen this**
16:06:38 **afterwards again. It reflects the fact that HOE140 was a**
16:06:45 **scientific breakthrough and a celebrated success.**
16:06:48 Q. **Dr. Wirth, if you would please now turn to PTX-061.**
16:07:00 **That is the German document. And its translation is**
16:07:02 **provided at PTX-061T.**
16:07:09 **Dr. Wirth, if you would turn your attention to**
16:07:13 **the English version, that is PTX-061T. Do you recognize**
16:07:18 **what is being described in that document?**
16:07:22 A. **Yes. It's the minutes of an internal scientific**
16:07:28 **meeting of the so-called scientific working group.**
16:07:33 Q. **And if you refer to Page PTX-061T.3, there is a list**
16:07:40 **of speakers at this meeting. The last name listed is Herr**
16:07:45 **Dr. Wirth. To whom does Herr Dr. Wirth refer?**
16:07:49 A. **It's me.**
16:07:50 Q. **What was the purpose of the 258th Meeting of the**
16:07:52 **Scientific Working Group Pharmaceuticals?**
16:07:55 A. **Researchers would be sent, the focus of this meeting**
16:08:01 **is on new projects and therefore it is called scientific**
16:08:06 **working groups.**
16:08:07 Q. **Are meeting minutes like PTX-061 something that**
16:08:11 **Hoechst would generate as part of its ordinary course of**
16:08:15 **business?**

16:08:15 A. **Yes.**

16:08:16 Q. **Did Hoechst maintain minutes like PTX-061 as part of its ordinary course of business?**

16:08:20 A. **Yes.**

16:08:22 Q. **If you would please turn to the last page of this document, Dr. Wirth, it is PTX-061T.10. If you look at the distribution list, it includes something called the WIAK spokesman. Were you a WIAK spokesman?**

16:08:25 A. **Yes.**

16:08:31 Q. **So would you have received these meeting minutes identified as PTX-061?**

16:08:36 A. **Yes.**

16:08:39 Q. **Dr. Wirth, please turn to page PTX-061T.6. We are at the bottom of the page. There is a heading, Biology (Dr. Wirth.) Is this referring to you?**

16:08:39 A. **Yes.**

16:08:42 Q. **Why are you being referred to in this heading at PTX-061T.6?**

16:08:45 A. **It's because I gave a presentation on the pharmacology of HOE140.**

16:08:46 Q. **Would you please turn to the next page, which is PTX-061T.7. I would refer you to the middle of the page, at the paragraph beginning with the subsection Discussion. What is discussion, if you know, referring to at this paragraph?**

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16:09:32 A. **It's the minutes here of the discussion which followed my presentation.**

16:09:36 Q. **If you would please read aloud the first two sentences of the paragraph beginning at the subsection discussion, which we will have highlighted on the screen?**

16:09:40 A. **"Nova is the only true competitor in this area (collaboration with Schering Plough). However, the company's antagonists have significantly shorter active times (2 minutes versus 80 minutes)."**

16:09:44 Q. **Dr. Wirth, what was the significance, if you know, of the comparison of the shorter active times referenced in the sentences you just read?**

16:09:48 **MR. WIESEN: Your Honor, I am going to object that this is calling for expert testimony. Asking for the significance of this comparison.**

16:09:50 **THE COURT: Counsel.**

16:09:54 **MS. KUZMICH: I think we are trying to establish that Dr. Wirth knew the competitor situation and that he is able to confidently comment on what the competitors were doing.**

16:09:57 **MR. WIESEN: The way she phrased the question was asking for expert testimony.**

16:10:00 **THE COURT: Rephrase it.**

16:10:05 **BY MS. KUZMICH:**

16:10:07 Q. **Dr. Wirth, do the two sentences that you read aloud**

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16:10:43 **that are highlighted in yellow reflect your understanding of**
16:10:46 **the differences between the compounds from Nova and the**
16:10:52 **other compounds that you referred to?**
16:10:54 A. **Yes. The Nova compound was extremely short-acting and**
16:10:58 **translated to a human situation it could easily be with two**
16:11:02 **minutes of duration of action. Who would take a drug with a**
16:11:05 **duration of action of two minutes? HOE140 had active**
16:11:13 **duration of action of here 80 minutes. And this correlates**
16:11:17 **well with the duration of action in animal models and also**
16:11:22 **in man. So it is a drug.**
16:11:25 Q. **Dr. Wirth, would you please now read aloud the last**
16:11:29 **sentence in the paragraph again at the subsection Discussion**
16:11:32 **on page PTX-061T.7?**
16:11:37 A. **"To further secure the patent situation, additional**
16:11:40 **tests with longer acting compounds ('sticky compounds') are**
16:11:48 **being performed."**
16:11:49 Q. **What are the sticky compounds that are mentioned in**
16:11:52 **the sentence you just read allowed?**
16:11:54 A. **Sticky compounds are compounds that have the very**
16:11:59 **tight binding to the receptor and therefore have a long**
16:12:02 **duration at the receptor. And additionally, the tight**
16:12:08 **binding could also reduce the enzymatic degradation and**
16:12:12 **increase the metabolic stability because the compound bound**
16:12:15 **to the receptor is not easily accessible to the degrading**
16:12:21 **enzymes.**

16:12:03 Q. **Dr. Wirth, were you personally involved in the testing of sticky compounds that are referenced in this sentence here?**

16:12:10 A. **Yes.**

16:12:10 Q. **And how were you personally involved in it?**

16:12:11 A. **I proposed -- it was my proposal to make a sticky compound, and chemists can engage in providing a compound, and I tested the compounds they made.**

16:12:16 Q. **And, Dr. Wirth, why did you refer to them as sticky compounds?**

16:12:20 A. **These compounds are called sticky because they stick to the receptor. It means they have a very tight binding, so they do not dissociate easily, and this enhances the efficacy and particularly their duration of action.**

16:12:23 Q. **And you said that you were involved in the testing and the designing of this project and these compounds; is that right?**

16:12:27 A. **Yes. My proposal.**

16:12:31 Q. **What did you propose for the sticky compounds in terms of making them sticky?**

16:12:31 A. **I proposed to make them sticky. How they were made sticky, this was the decision and the task of the chemist, and he decided to use lipophilic bulky moieties, which he attached to the N-terminus.**

16:12:36 **MR. WIESEN: Objection. Hearsay, Your Honor.**

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16:13:22 **THE COURT: Okay. Sustained.**

16:13:29 **BY MS. KUZMICH:**

16:13:30 Q. **Was icatibant one of the sticky compounds that**
16:13:32 **you referenced, or excuse me, that is referenced on**
16:13:36 **PTX-061T?**

16:13:37

16:13:37 A. **No.**

16:13:38 Q. **Dr. Wirth, referring back to the statement, to further**
16:13:43 **secure the patent situation, additional tests with longer**
16:13:47 **acting compounds are being performed, what, if you know, was**
16:13:53 **meant by the reference to securing the patent situation?**

16:13:55 A. **At a meeting in my presentation, I always showed**
16:14:01 **results with sticky compounds so as to demonstrate a**
16:14:04 **feasibility, and we received the approval from the**
16:14:11 **scientific working group to continue the work and to be able**
16:14:15 **to file a patent.**

16:14:16 Q. **Dr. Wirth, do you know if your work on sticky**
16:14:19 **compounds was ever patented?**

16:14:21 A. **Yes.**

16:14:22 Q. **Dr. Wirth, if you would now please turn to DTX-59 in**
16:14:28 **your binder, and that is U.S. Patent No. 5,597,803.**

16:14:37 **And, Dr. Wirth, do you recognize this document?**

16:14:40 A. **Yes. Patent No. 5,597,803.**

16:14:44 Q. **And are you an inventor on the 5,597,803, Doctor?**

16:14:49 A. **Yes.**

16:14:50 Q. **Is it acceptable to you if we refer to this patent,**
16:14:55 **which is labeled DTX-59, as the '7,803 patent?**
16:15:00 A. **Yes.**
16:15:00 Q. **Dr. Wirth, what is the title of the '7,803 patent?**
16:15:04 A. **Bradykinin peptides with modifications at the**
16:15:11 **N-terminus.**
16:15:11 Q. **What is your understanding of the subject matter that**
16:15:13 **is disclosed in the '7,803 patent?**
16:15:17 A. **The patent discloses bradykinin with N-terminus**
16:15:23 **modification with lipophilic moiety so as to increase the**
16:15:29 **binding so as to make sticky compounds. The purpose is to**
16:15:32 **get much tighter binding, which would increase the efficacy**
16:15:35 **and the duration of action of these drugs.**
16:15:39 Q. **What was your involvement in the subject matter of the**
16:15:42 **'7,803 patent?**
16:15:42 A. **It was -- this project was my proposal, my initiative,**
16:15:50 **to make compounds, and I tested them and I wrote the**
16:15:53 **reports.**
16:15:53 Q. **Dr. Wirth, can you please point to the data in the**
16:15:59 **'7,803 patent that you were conducting the pharmacological**
16:16:05 **testing of, that you personally conducted?**
16:16:08 A. **Yes. Table 2.**
16:16:11 Q. **Table 2, Dr. Wirth?**
16:16:14 A. **Yes. Table 2 shows the washout time at the T50 value,**
16:16:20 **which means the time one half of it has decayed. So it's a**

measure, best measure of the binding to the receptor. The longer the time is, the tighter the binding.

Q. Dr. Wirth, is the subject matter of the '7,803 patent in any -- in any way related to the sticky compounds that we were discussing a few minutes ago at PTX-061?

A. Yes.

Q. And how is that subject matter related between the '7,803 patent, which is DTX-59, and PTX-061?

A. Here, we report -- here, we disclose the compounds and show the results about a compound I mentioned from this scientific meeting.

Q. And, Dr. Wirth, if you would please turn to Example one of the '7,803 patent, which is at Column 1, line 44. And does that peptide in Example 1 of the '7,803 patent represent a sticky compound?

A. Yes, it is.

Q. And how do you understand what makes it sticky? What is it?

A. The attachment of Fmoc, which is a lipophilic moiety.

Q. And is icatibant an N terminally modified peptide?

A. No, it is not.

MS. KUZMICH: No further questions at the moment, Your Honor.

THE COURT: All right. Mr. Wiesen?

Your Honor, if we can distribute a binder?

16:17:52 **THE COURT: Yes.**

16:18:10 **(Binders handed to the Court and to the**

16:18:12 **witness.)**

16:18:48 **CROSS-EXAMINATION**

16:18:50 **BY MR. WIESEN:**

16:18:55 Q. **Good afternoon. You pronounce it Dr. Wirth?**

16:18:58 A. **Good afternoon.**

16:18:59 Q. **Can you turn to DTX-59? It's in either of the binders**

16:19:06 **you have. It's the '7,803 patent you were just looking at.**

16:19:14 **And I want to go back to that Table 2 you just finished with**

16:19:18 **Ms. Kuzmich. DTX-59-9, the left-hand column. There we go.**

16:19:26 **We just pulled it up there.**

16:19:29 **This first compound you discussed, you**

16:19:34 **agree that this is Fmoc and then the ten amino acids of**

16:19:38 **icatibant?**

16:19:39 A. **Yes.**

16:19:41 Q. **And that's the reason you made the compound. It came**

16:19:44 **after icatibant; is that correct?**

16:19:46 A. **Yes.**

16:19:46 Q. **And you added the Fmoc onto the icatibant; is that**

16:19:50 **right?**

16:19:51 A. **Yes.**

16:19:52 Q. **And that's how you developed this compound,**

16:19:55 **recognizing that it started with icatibant; is that right?**

16:19:58 A. **Yes.**

16:19:59 Q. **All right. We can take that down.**

16:20:02 **I want to make sure you understand what your**
16:20:06 **responsibilities were at Hoechst. You joined the bradykinin**
16:20:10 **project you think in maybe 1989 or 1990; is that right?**
16:20:14 A. **Yes.**
16:20:14 Q. **And by that point, icatibant had been synthesized; is**
16:20:18 **that correct?**
16:20:18 A. **Yes.**
16:20:18 Q. **It had already been identified for development;**
16:20:21 **right?**
16:20:22 A. **Yes.**
16:20:23 Q. **And you don't know who first came up with the idea for**
16:20:28 **the compound icatibant; right?**
16:20:29 A. **The inventors on the patent.**
16:20:34 Q. **But you do not know which one of them?**
16:20:36 A. **I mean, all inventors.**
16:20:38 Q. **And then your job was to test the, do pharmacological**
16:20:44 **tests for bradykinin antagonists; is that correct?**
16:20:46 A. **Yes, but I was not -- I was not involved because I**
16:20:51 **wasn't part of the project. I joined later on to perform**
16:20:54 **additional studies, more -- pharmacologic studies.**
16:21:00 Q. **Do you know how many bradykinin antagonist peptides**
16:21:03 **were made as part of the bradykinin antagonist project at**
16:21:06 **Hoechst?**
16:21:07 A. **A lot. I don't remember the number.**

16:21:09 Q. **Dozens? Hundreds?**

16:21:12 A. **Probably, yes.**

16:21:13 Q. **And for all of those, was the process at Hoechst that first the compound would be made and then it would be tested in vitro, and then if there was in vitro activity, it would be tested in vivo?**

16:21:27 A. **Yes.**

16:21:28 Q. **And you were in charge of that project once you joined the bradykinin task?**

16:21:32 A. **Most of these compounds had already been tested and Hoe 140 identified.**

16:21:41 Q. **By the time Hoe 140 was identified, how many bradykinin antagonists had been made and tested by in vitro and in vivo testing at Hoechst?**

16:21:51 A. **It was a very small amount because the project had been finished, and when you have a development compound, a compound that is used for development, you do only a little work, so the majority of the work had been done before.**

16:22:05 Q. **Sorry. I think I phrased the question badly. How many had been completed -- how many compounds had been made, tested in vitro and tested in vivo before Hoe 140?**

16:22:16 A. **I don't -- I didn't take part. I don't know. I wasn't part of the team at that time. No, I can't say.**

16:22:24 Q. **Have you seen those reports in your time at Hoechst?**

16:22:27 A. **I mean, there are no official -- there are no reports.**

16:22:31 **These are documented in printed forms for each -- for each**
16:22:35 **compound in printed form, which the compound, which you give**
16:22:39 **to the chemist, which you give to the team.**
16:22:41 Q. **Again, fair to say dozens of compounds that were**
16:22:45 **made?**
16:22:46 **MS. KUZMICH: Objection. Asked and answered.**
16:22:47 **THE COURT: Sustained. Sustained.**
16:23:00 **BY MR. WIESEN:**
16:23:00 Q. **Can you turn in your binder to DTX-50. You're**
16:23:11 **familiar with this paper; is that correct?**
16:23:12 A. **Yes, I'm familiar with it.**
16:23:14 Q. **You are the first author on this paper; is that right?**
16:23:16 A. **Yes.**
16:23:16 Q. **It reports in vivo studies with icatibant; is that**
16:23:22 **right?**
16:23:22 A. **Yes.**
16:23:23 Q. **And if we turn to the last page, DTX-50.04, we look at**
16:23:35 **the date that it was submitted. It was first submitted**
16:23:40 **July 25th, 1990; is that correct?**
16:23:42 A. **That's what it says.**
16:23:44 Q. **And so does that mean that you would have had all of**
16:23:47 **the in vivo data reported hereby July 25th, 1990?**
16:23:52 A. **All the data that are reported here first.**
16:23:57 Q. **And actually had the data earlier than that; right,**
16:24:00 **sir?**

16:24:01 A. **Yes, but not all. There were other data that are not**
16:24:03 **reported here.**
16:24:04 Q. **But all the data that are reported here, you had**
16:24:07 **before July 25th, 1990; right?**
16:24:11 A. **Mm-hmm.**
16:24:12 Q. **And some of the data here you had as early as March of**
16:24:14 **1989; is that right?**
16:24:16 A. **Yes.**
16:24:21 Q. **All right. If we go to PTX-12, that was the green**
16:24:26 **file you looked at with Ms. Kuzmich; is that right? Do you**
16:24:33 **have that in your binder? PTX-12 was the collection of**
16:24:39 **reports on the pharmacology results; is that correct?**
16:24:41 A. **Mm-hmm.**
16:24:44 Q. **If we go to PTX-12.140, this is the evaluation of the**
16:25:20 **biological half-life of, the number is given, icatibant, and**
16:25:26 **given by intraarterial infusion in comparison to another**
16:25:30 **drug in this anesthetized rats. Right?**
16:25:33 A. **Sorry. Could you repeat that?**
16:25:35 Q. **Did I read the title correctly?**
16:25:37 A. **Yes.**
16:25:41 Q. **And this data was generated from August 30th to**
16:25:45 **December 14th, 1989. Right?**
16:25:47 A. **That's what it says.**
16:25:48 Q. **And if you go back to DTX-50, your paper, and we turn**
16:25:57 **to DTX-50.2, that's the same study that is reported there,**

16:26:07 **the interarterial infusion of bradykinin antagonists.**

16:26:11 **Right?**

16:26:11 A. **I can't read it here. Can you highlight it?**

16:26:17 Q. **The title and then this first interarterial infusion**

16:26:21 **of bradykinin antagonists.**

16:26:34 A. **It was certainly an interarterial infusion, yes.**

16:26:44 **THE COURT: Are you two together?**

16:26:45 **MR. WIESEN: I think he is trying to figure out**

16:26:51 **where on the paper.**

16:26:52 **THE COURT: Why don't you help him.**

16:26:54 **BY MR. WIESEN:**

16:26:54 Q. **You see this talks about an equimolar dose of .75**

16:27:01 **nanomole infused over five minutes and talks about**

16:27:03 **impairment by 71 percent. Do you see that?**

16:27:05 A. **Yes.**

16:27:05 Q. **If we go back to PTX-12.142, and put those up side by**

16:27:16 **side, so we have on the right the report from 1989, and on**

16:27:28 **the left we have your 1991 paper. Do you see that?**

16:27:36 A. **Yes.**

16:27:36 Q. **So does this confirm that you had this in vivo data by**

16:27:40 **1989 at Hoechst?**

16:27:53 A. **I can't remember the dates of the report.**

16:27:57 Q. **Let's do it this way. Do you agree that this report**

16:28:01 **on the left at PTX-12.142 appears to be the internal report**

16:28:07 **that corresponds with the results reported in DTX --**

16:28:12 **THE COURT: Do you mean the right or the left?**

16:28:13 **MR. WIESEN: Sorry.**

16:28:16 **BY MR. WIESEN:**

16:28:16 Q. **That PTX-12.142 on the right corresponds with the same data reported on the left in the paper DTX-50?**

16:28:22

16:28:27 A. **Yes.**

16:28:27 Q. **Then if we go back just to PTX-12.140, and we look at the date, the investigational period for that data was August to December of 1989. Correct?**

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16:28:58 A. **It's what it says.**

16:28:59 Q. **So Hoechst had that in vivo data for icatibant in 1989. Right?**

16:29:05

16:29:07 A. **Yes.**

16:29:07 Q. **Let's look at one other. If you go to 12.160. We pull out the very top of this. This is the internal report with the language -- with the date at the top, please, Mr. Chase. Thank you.**

16:29:29

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16:29:38 **This is the internal report for March 31, 1989 on anti-inflammatory effect in the carrageenan paw edema in rats. Correct?**

16:29:44

16:29:49

16:29:50 A. **Correct.**

16:29:52 Q. **That is another in vivo model you use for bradykinin antagonism. Right?**

16:29:55

16:29:57 A. **Yes.**

16:29:57 Q. **And if we look at the bottom half of this page,**

16:30:03 12.160, and we pull out the results, and we compare that to
16:30:11 the results that are at the bottom of DTX-50.3 in the Wirth
16:30:17 paper, Dr. Wirth, do you agree that the results that are
16:30:22 reported in that March 1989 report are the same as the
16:30:25 results in the carrageenan paw edema in rats in DTX-50, the
16:30:36 Wirth 1991 paper?
16:30:37 A. Yes.
16:30:38 Q. Hoechst had those results by 1989 as well. Right?
16:30:42 A. Yes.
16:31:04 Q. Take those down.
16:31:28 Dr. Wirth, when you started on the bradykinin
16:31:30 antagonist project you came to understand how Hoechst got
16:31:33 started on the project. Correct?
16:31:35 A. I learned how it started, yes.
16:31:37 Q. It started by someone going to a conference. Right?
16:31:40 A. Right.
16:31:40 Q. Who was that?
16:31:43 A. I don't know exactly, but probably a chemist first and
16:31:48 then pharmacologist. I don't know who was first.
16:31:52 Q. And they went to a conference and heard Dr. Stewart
16:31:55 speak. Correct?
16:31:56 A. Yes.
16:31:56 Q. And they learned about bradykinin antagonists from Dr.
16:32:01 Stewart's work?
16:32:01 A. They learned about this work.

16:32:03 Q. **And then they started Hoechst's project based on the**
16:32:08 **work that they learned about that was published by Dr.**
16:32:11 **Stewart. Correct?**
16:32:12 **MS. KUZMICH: Objection. Hearsay.**
16:32:15 **THE COURT: Rephrase your question, please.**
16:32:18 **BY MR. WIESEN:**
16:32:19 Q. **I think I asked if they learned about the work from**
16:32:26 **Dr. Stewart in the project they were working on?**
16:32:30 **MS. KUZMICH: Objection. Who are you referring**
16:32:32 **to as they?**
16:32:33 **THE COURT: Could you put a more precise**
16:32:35 **question.**
16:32:35 **MR. WIESEN: Yes, Your Honor.**
16:32:36 **BY MR. WIESEN:**
16:32:36 Q. **When you started on the project, did you communicate**
16:32:41 **with others on the team about how the project got started at**
16:32:45 **Hoechst, on the bradykinins project?**
16:32:49 A. **Because we were talking often about this project.**
16:32:52 **This is what I heard. Maybe it's more rumor than exact**
16:32:58 **information.**
16:32:58 Q. **Did you personally review any publications or**
16:33:01 **literature from Dr. Stewart?**
16:33:03 A. **No.**
16:33:27 Q. **Dr. Wirth, when you started on the bradykinin**
16:33:30 **antagonist project, Hoechst didn't have any particular**

16:33:33 **indications in mind. Correct?**

16:33:36 A. **No. It was already -- went already in the direction**

16:33:42 **of something, we had discussion. The discussions go on and**

16:33:46 **at a certain point a decision is made. It slowly starts,**

16:33:49 **discussion is discussion and at a certain point a decision**

16:33:52 **is made.**

16:33:53 Q. **At that initial time, hereditary angioedema was not**

16:33:56 **one of the indications being discussed?**

16:33:58 A. **It was one possibility. It was a possibility.**

16:34:03 Q. **But it wasn't one of the indications that was being**

16:34:05 **discussed at Hoechst, was it?**

16:34:07 A. **It was not discussed for development at that time.**

16:34:11 Q. **And you couldn't have predicted it would work in**

16:34:14 **hereditary angioedema. Right?**

16:34:16 A. **You could not --**

16:34:18 **MS. KUZMICH: Objection. I think we are calling**

16:34:20 **for expert testimony here.**

16:34:21 **THE COURT: Sustained.**

16:34:22 **MR. WIESEN: Fair enough, Your Honor.**

BY MR. WIESEN:

16:34:24 Q. **Dr. Wirth, you did not predict that it would work in**

16:34:28 **hereditary angioedema at the time. Correct?**

16:34:32 A. **You can't predict this. You must test it. I mean,**

16:34:36 **most predictions are wrong in the pharmaceutical industry.**

16:34:39 **That is why it is so difficult.**

16:34:49 Q. **You spoke a little on direct about Nova. Do you**
16:34:53 **recall that?**
16:34:56 A. **Yes.**
16:34:57 Q. **You and Hoechst were aware that Nova Pharmaceuticals**
16:35:01 **had licensed bradykinin antagonists from Dr. Stewart.**
16:35:04 **Correct?**
16:35:05 A. **Yes.**
16:35:05 Q. **That was public knowledge. Right?**
16:35:07 A. **Yes.**
16:35:07 Q. **You and your colleagues -- well, you knew that Nova**
16:35:12 **was working at one point with SmithKlineBeecham. Correct?**
16:35:17 A. **Yes.**
16:35:17 Q. **You personally have never had any contacts with Nova.**
16:35:23 **Right?**
16:35:23 A. **Yes. I had no contact with them.**
16:35:25 Q. **You know some of your colleagues did?**
16:35:27 A. **The chemists may have had contacts, because there were**
16:35:31 **meetings and you meet people.**
16:35:39 Q. **If you would turn to PTX-61 or 61T, so we can use the**
16:35:56 **English translation. You discussed these meeting minutes on**
16:36:08 **direct. Correct?**
16:36:09 A. **Yes.**
16:36:09 Q. **These were from a meeting dated October 30th, 1991.**
16:36:16 **Correct?**
16:36:17 A. **Yes.**

16:36:17 Q. **You looked with Ms. Kuzmich at PTX-61T.7. Right?**

16:36:28 A. **Sorry?**

16:36:29 Q. **61T.7, a particular page, we will pull it up. In the middle --**

16:36:34 A. **Yes, this is the discussion that followed the presentation.**

16:36:36 Q. **Can we pull up the discussion here in the middle of the page?**

16:36:38 A. **Yes.**

16:36:41 Q. **You discuss that Nova is the only true competitor in this area. Right?**

16:36:42 **So as of October 1991, at least, Nova was still viewed as a competitor. Is that right?**

16:36:43 A. **As a competitor, they had compounds in development. It seemed they had compounds in development. So they were competitors.**

16:36:49 Q. **Nova was still trying to develop bradykinin antagonists as far as you knew at Hoechst in October 30th, 1991. Right?**

16:36:53 A. **Yes.**

16:36:58 Q. **If you go back to PTX-61T.5, if we could pull out this whole paragraph that is not redacted on the page. You see the last two sentences say, -- first it says, "HOE140 has a good chance to qualify for patent protection."**

16:37:02 **Do you see that?**

16:37:05

16:37:05

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16:37:44 A. **Yes.**

16:37:44 Q. **And then -- did you write this section, by the way?**

16:37:50 A. **I am sorry?**

16:37:51 Q. **Did you write this portion of the document?**

16:37:54 A. **No, I didn't.**

16:37:57 Q. **After talking about patent protection, it says, "The only known competitor at this time is Nova."**

16:38:05 **Do you see that?**

16:38:05 A. **Yes.**

16:38:06 Q. **At Hoechst, did you discuss patents and Nova at the same time?**

16:38:10 A. **I am not -- I had nothing to do with these patents because I am a pharmacologist. It was not my task. Patents were not my task.**

16:38:28 Q. **You can take that down.**

16:38:52 **THE COURT: Do you have a question, Mr. Wiesen?**

16:38:53 **MR. WIESEN: I am going through my notes, Your Honor, to see whether we can wrap this up more quickly.**

16:38:59 **THE COURT: That would be great.**

16:39:00 **MR. WIESEN: Can I have a moment?**

16:39:02 **THE COURT: Yes.**

16:39:09 **MR. WIESEN: No further questions, Your Honor.**

16:39:12 **MS. KUZMICH: No redirect, Your Honor.**

16:39:14 **THE COURT: Doctor, please be careful stepping down.**

16:39:17

(Witness excused.)

16:39:28 THE COURT: What do we have next, Mr. Haug?

16:39:30 MR. HAUG: We have depositions which we don't want to play now at 4:30. If I may, I will tell you what we have going tomorrow?

16:39:44 We have a very short deposition clip of a regulatory person, maybe 15 minutes. We have a longer clip of one of the scientists from Nova. That one is a little longer. Close to an hour, about an hour. That's it for depositions for us.

16:39:57 We will have our main expert, technical expert, professor Walensky, tomorrow. And will continue on with more witnesses depending --

16:40:02 THE COURT: So there is no expert that you want to call right now that you can qualify.

16:40:06 MR. HAUG: No.

16:40:08 THE COURT: I think we will call it a day.

16:40:10 (Court recessed.)

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